

SCUOLA DI SCIENZE

Dipartimento di Chimica Industriale "Toso Montanari"

Corso di Laurea Magistrale in

**Chimica Industriale**

Classe LM-71 - Scienze e Tecnologie della Chimica Industriale

**Organocatalytic Enantioselective Vinylogous Aldol-  
Lactonization Cascade Reaction of 3-Alkylidene Oxindoles to  
Trifluoromethyl Ketones**

Tesi di laurea sperimentale

**CANDIDATO**

Giada Belletti

**RELATORE**

Dott.ssa Emanuela Marotta

**CORRELATORI**

Dr. Giorgio Bencivenni

Dr. Simone Crotti



## ABSTRACT

In this work, an highly enantioselective vinylogous aldol-lactonization cascade reaction of 3-alkylidene oxindole to  $\alpha,\beta$ -unsaturated trifluoromethyl ketone, promoted by bifunctional organocatalysts, is presented. The reaction proceed through 1,2-addition followed by cascade lactonization to afford an unsaturated lactone bearing a chiral trifluoromethylated tetrasubstituted carbon stereocenter with high enantioselectivity and moderate yield. Nevertheless, also the two E/Z isomers of the correspondent 1,2-addition product are obtained.

Argomento di questo lavoro è l'addizione viniloga enantioselettiva tra 3-alciliden ossindoli e trifluorometil chetoni  $\alpha,\beta$ -insaturi, promossa da catalizzatori bifunzionali. La reazione procede attraverso 1,2-addizione e successiva lattonizzazione per ottenere, con alta enantioselezione e resa moderata, un lattone insaturo contenente un centro chirale quaternario contenente un gruppo trifluorometilico. Tuttavia, dalla reazione si ottiene anche la miscela E/Z del corrispondente prodotto di 1,2-addizione.



# SUMMARY

1. INTRODUCTION.....	1
1.1. Chirality and asymmetric synthesis.....	1
1.2. Axial chirality.....	3
1.3. Asymmetric organocatalysis: aminocatalysis and activation strategies.....	5
1.3.a. Enamine catalysis.....	6
1.3.b. Iminium-ion catalysis.....	8
1.3.c. Tandem catalysis.....	9
1.3.d. Dienamine catalysis.....	10
1.3.e. Somo catalysis.....	11
1.3.f. Advantages and limits of organocatalysis.....	11
1.4. Bifunctional organocatalysis.....	12
1.4.a. Cinchona alkaloids.....	12
1.4.b. Thiourea organoderivatives.....	15
1.5. Vinylogy.....	17
1.6. The substrates: oxindoles and 3-alkylidene oxindoles.....	19
1.7. The substrates: $\alpha,\beta$ -unsaturated trifluoromethyl ketones.....	26
2. AIMS OF THE RESEARCH PROJECT.....	30
3. RESULTS AND DISCUSSION.....	32
3.1. Synthesis of the substrates.....	32
3.2. Preliminary reaction tests.....	33
3.3. NMR studies and identification of the products.....	35
3.4. HPLC analysis of the racemic product 3 e 4.....	41
3.5. Screening of the catalyst.....	43
3.6. Screening of the solvent.....	49
3.7. Screening of reaction conditions.....	51
3.8. Studies on the reaction mechanism.....	55
3.9. Reactivity towards 1,1,1-trifluoroacetophenone.....	59
3.10. Investigations on the hypervinylogous addition of 3-alkylidene oxindoles to unsaturated trifluoromethyl ketones.....	61
4. CONCLUSIONS AND FUTURE WORK.....	63
5. EXPERIMENTAL SECTION.....	64

5.1 General informations .....	64
5.2. Synthesis of (e)-1,1,1-trifluoro-4-phenylbut-3-en-2-one <sup>60</sup> .....	65
5.3. Synthesis of synthesis of 3-(propan-2-ylidene)indolin-2-one <sup>58</sup> .....	65
5.4. Synthesis of tert-butyl 2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate .....	66
5.5. Synthesis of dihydroquinine thiourea.....	66
5.6. General procedure for the addition between 2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate and (e)-1,1,1-trifluoro-4-phenylbut-3-en-2-one .....	67
5.7. Synthesis of (e)-1,1,1-trifluoro-4-(2-oxoindolin-3-ylidene)-2-phenylpentan-2-yl acetate and (z)-1,1,1-trifluoro-4-(2-oxoindolin-3-ylidene)-2-phenylpentan-2-yl-acetate .....	68
5.8. Synthesis of 2-methyl-3,5-dinitrobenzaldehyde .....	68
5.9. Synthesis of (e)-tert-butyl 3-(2-methyl-3,5-dinitrobenzylidene)-2-oxoindoline-1-carboxylate .....	69
5.10. General procedure for addition between 2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate and 2,2,2-trifluoroacetophenone.....	70
5.11. Data of the products .....	71
6. REFERENCES.....	76

## ABBREVIATIONS AND SYNONYMS

**Boc<sub>2</sub>O**: Di-tert-butyl-carbonate

**DCM**: Dichloromethane

**DEPT**: Distortionless Enhancement by Polarization Transfer

**DHQA**: Dihydroquinine

**DHQA-thiourea**: 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1S)-((2R,4S,5R)-5-ethylquinuclidin-2-yl)(6-hydroxyquinolin-4-yl)methyl)thiourea

**DHQA-squaramide**: 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((1S)-((1S,2S,4S)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione

**DIPE**: Diisopropyl ether

**DMF**: Dimethylformamide

**DMAP**: 4-dimethylaminopyridine

**DMSO**: Dimethyl sulfoxide

**dr**: Diastereomeric ratio

**EA**: Ethyl acetate

**ee (%)**: Enantiomeric excess

**ETOH**: Ethanol

**EWG**: Electron withdrawing group

**E**: Electrophile

**HOMO**: Highest occupied molecular orbital

**LUMO**: Lowest unoccupied molecular orbital

**MBH**: Morita-Baylis-Hillman

**MS**: Molecular sieves

**MTBE:** Methyl tert-butyl ether

**NMR:** Nuclear magnetic resonance

**NOESY:** Nuclear Overhauser Effect Spectroscopy

**Nu:** Nucleophile

**QA:** Quinine

**QA-thiourea:** 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1S)-(6-methoxyquinolin-4-yl)((1S,2S,4S)-5-vinylquinuclidin-2-yl)methyl)thiourea

**QDA:** Quinidine

**QDA-thiourea:** 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R)-(6-methoxyquinolin-4-yl)((1R,2R,4R)-5-vinylquinuclidin-2-yl)methyl)thiourea

**QDA-squaramide:** 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((1R)-(6-methoxyquinolin-4-yl)((1R,2R,4R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione

**SOMO:** Singly Occupied Molecular Orbital

**Takemoto Catalyst:** 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R)-2(dimethylamino)cyclohexyl)thiourea

**THF:** Tetrahydrofuran

**TLC:** Thin Layer Chromatography

**TMS:** Tetramethylsilane

**HPLC:** High Pressure Liquid Chromatography

**PG:** Protecting group

**PCC:** Pyridinium chlorochromate

**RT:** Room temperature



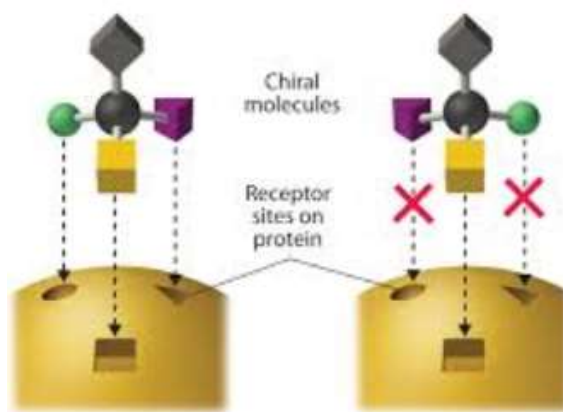
# 1. INTRODUCTION

## 1.1. CHIRALITY AND ASYMMETRIC SYNTHESIS

Chirality is a geometric property of molecules which are not superimposable on their mirror image and can therefore exist as two enantiomers. Indeed, the term chirality is derived from the Greek word for hand, χείρ (kheir) because hands have no plane of symmetry and a left hand is not superimposable on its mirror image (a right hand).

In 1848, chiral chemistry was identified for the first time by Louis Pasteur<sup>1</sup> when he separated the two isomers of sodium potassium tartrate. He discovered that the two isomers were different in their ability to rotate plane polarized light, even if they were identical in physiochemical properties.

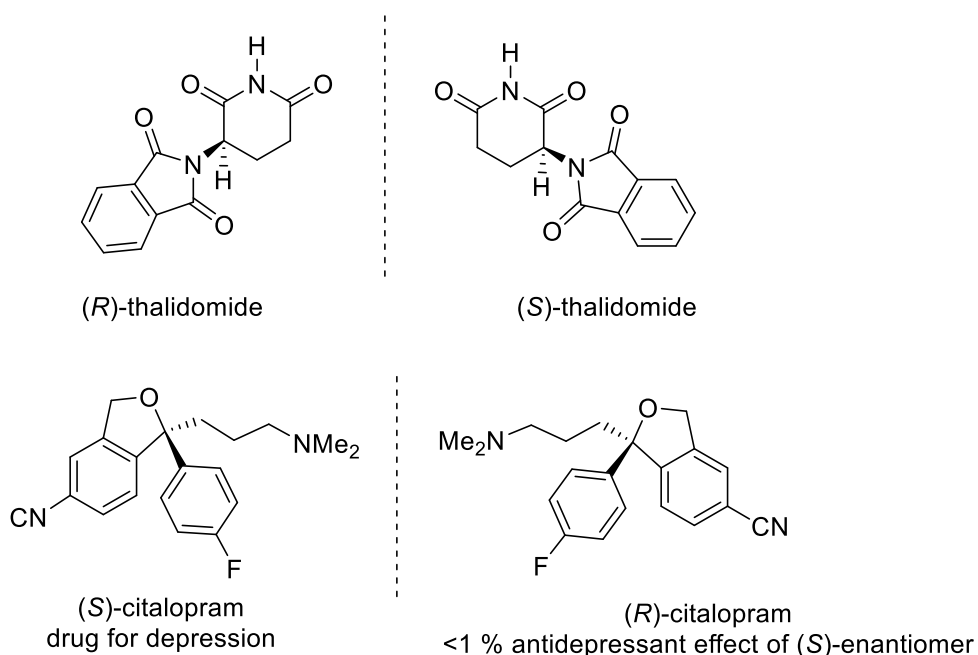
Enantiomeric forms are founded in many organic and inorganic substances; also, biomolecules such as proteins, which are responsible for the structure and regulation of cells, possess enantiomeric forms.



**Fig. 1:** Interaction of two enantiomers with a chiral biological receptor.

Two enantiomers are identical until they are placed in a chiral environment. For instance, it is possible to observe that in Fig.1 only one enantiomer fits the receptor site leading to a response while, the other one, is not able to bind the receptor. Because of the chirality of the molecules that are involved, the biochemical processes are really sensible to enantiomeric forms. In particular, when a drug molecule is chiral, its two enantiomers can differ significantly in their activity. An example that has sadly become famous is the one of Thalidomide<sup>2</sup>, a

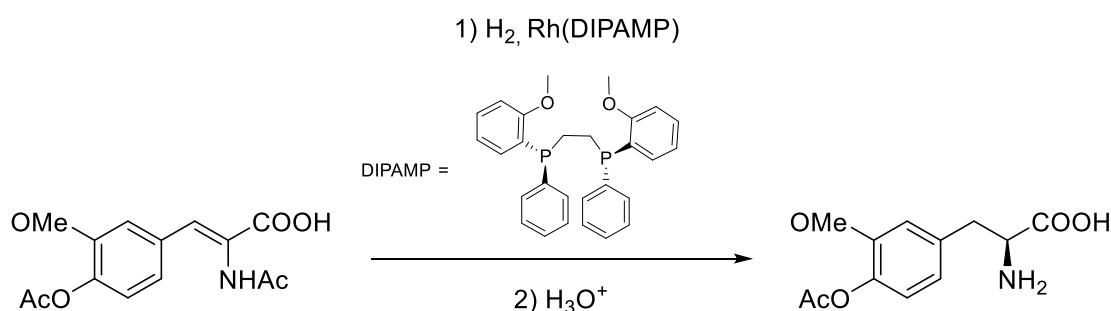
drug used in Germany during the fifties and sixties to alleviate morning sickness in pregnant women. Thalidomide (Fig. 2) is racemic and it has therefore equal amounts of the two enantiomers. Whilst (*R*)-thalidomide is the active substance of the drug and it has anti-nausea and sedative effects, (*S*)-thalidomide is teratogen and toxic for the fetus and caused the birth of babies with serious malformations. In other cases, only one of the two enantiomers of a drug molecule possesses activity: the antidepressant citalopram is marketed only as its *S* enantiomer because the *R* enantiomer is essentially inactive (Fig. 2).



**Fig. 2:** Enantiomeric forms of thalidomide and citalopram.

In the modern organic synthesis, the obtainment of enantiomerically enriched compounds has assumed a central role throughout the years, due to the different biological properties of enantiomers. There are several ways to afford enantio-enriched compounds; for instance, it is possible to exploit a collection of natural and enantiomerically pure substances, usually amino acids and carbohydrates, called *chiral pool*. The chirality of these molecules is then preserved in the remainder of the reaction sequences to obtain the product of interest. Alternately, *resolution* is a method that can be used to separate enantiomers. Resolution requires an enantiomerically pure resolving agent that is able to form a mixture of diastereoisomers, separable through chromatography or fractional crystallization. At the end of the process, both the enantiomers and the resolving agent are

recovered. Moreover, it is possible to exploit *chiral auxiliaries*, which are compounds temporary incorporated in the starting reagent. The auxiliary assists the substrate to react in a diastereoselective way, such that only one stereoisomer is allowed to form. Finally, the chiral auxiliary is removed from the product and it can be recycled. On the other hand, asymmetric catalysis is nowadays one of the most popular way to afford enantio-enriched compounds. In *asymmetric catalysis* an enantiopure catalyst direct the formation of one particular stereoisomer, through creation of diastereomeric transition states.



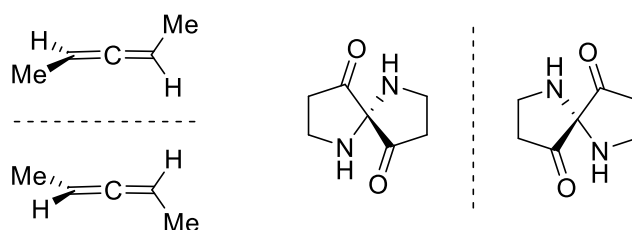
**Scheme 1:** Industrial synthesis of (*L*)-Dopa.

The first industrial synthesis of a chiral drug with the use of asymmetric catalysis was developed by William Knowles at Monsanto, who received the Nobel Prize in 2001<sup>3</sup>. This asymmetric hydrogenation, catalysed by chiral rhodium complexes, allow to synthesize (*L*)-Dopa, a drug used to treat Parkinson's disease (Scheme 1). While asymmetric catalytic hydrogenation and oxidation dominated the early years of the field, the scope of asymmetric catalysis have been extended to a wide range of reactions, such as the generation of chiral carbon centres through C-C bond forming reactions.

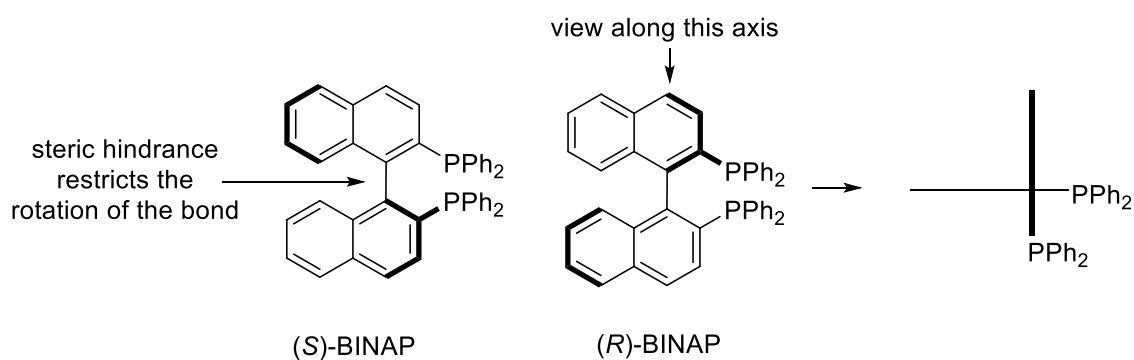
## 1.2. AXIAL CHIRALITY

Axial chirality is a particular case of chirality in which the molecule does not have a stereogenic centre but it possesses a stereogenic axis. Substituents are held around this axis in a spatial arrangement that it is not superimposable on its mirror image, for instance certain allene compounds and spiranes display axial chirality (Fig. 3). Similarity, axial chirality is observed in atropisomeric biaryls that

exist as two separate enantiomers due to the restricted rotation of the aryl-aryl bond like BINAP (Fig. 4).

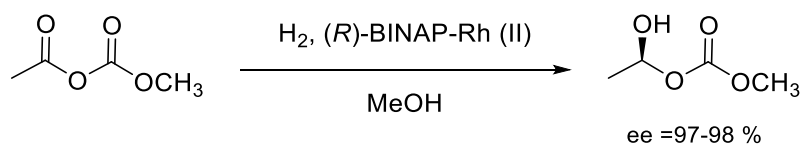


**Fig. 3:** Chiral allene at the left and chiral spiro compound at the right.



**Fig. 4:** Enantiomeric forms of BINAP.

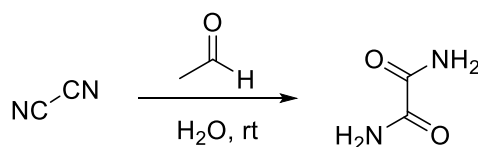
Indeed, atropisomeric biaryls have been widely used as chiral ligand in asymmetric synthesis. For example, in 1993, R. Noyori and his co-workers reported an asymmetric hydrogenation of 3-oxo carboxylates using BINAP-ruthenium complexes<sup>4</sup> (Scheme 2).



**Scheme 2:** Synthesis of (*R*)-methyl 3-hydroxybutanoate.

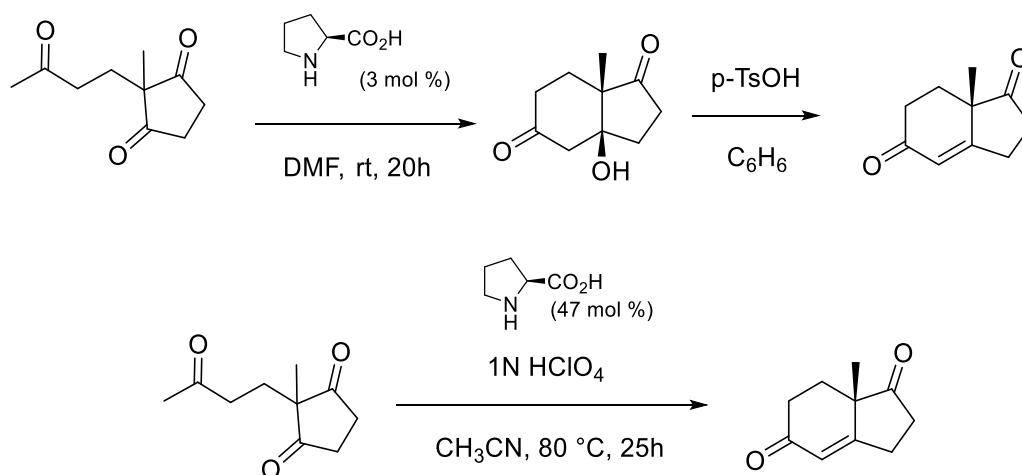
### 1.3. ASYMMETRIC ORGANOCATALYSIS: AMINOCATALYSIS AND ACTIVATION STRATEGIES

The term organocatalysis was first used in 2000 by David MacMillan to describe the use of chiral small molecules to catalyse organic transformations, with particular emphasis on asymmetric variants<sup>5</sup>. Organic molecules have been used as catalyst from the early age of synthetic chemistry. Indeed, the discovery of the first organocatalytic reaction is attributed to J. von Liebig. In 1860 Liebig found accidentally that dicyan is transformed into oxamide in the presence of an aqueous solution of acetaldehyde, which was further identified as the first “organocatalyst” (Scheme 3).



**Scheme 3:** Von Liebig's oxamide synthesis.

On the other hand, during the 20<sup>th</sup> century, there were only few reports on the use of small organic molecules as catalysts for asymmetric reactions. The most famous among them is the Hajos–Parrish–Eder–Sauer–Wiechert reaction, developed in the 1970's for steroid synthesis, which was a relevant topic at that time<sup>6</sup>. The reaction proceed to the asymmetric intramolecular aldol or directly to the dehydrated product under proline catalysis to obtain the Wieland-Miescher ketone, an useful intermediate in steroid synthesis (Scheme 4). Precisely, two different protocols for this reaction were reported by two industrial groups: Hajos and Parrish at La Roche<sup>7</sup> and Eder, Sauer and Wiechert at Schering<sup>8</sup>.

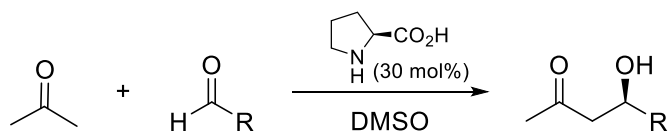


**Scheme 4:** Hajos–Parrish–Eder–Sauer–Wiechert reaction.

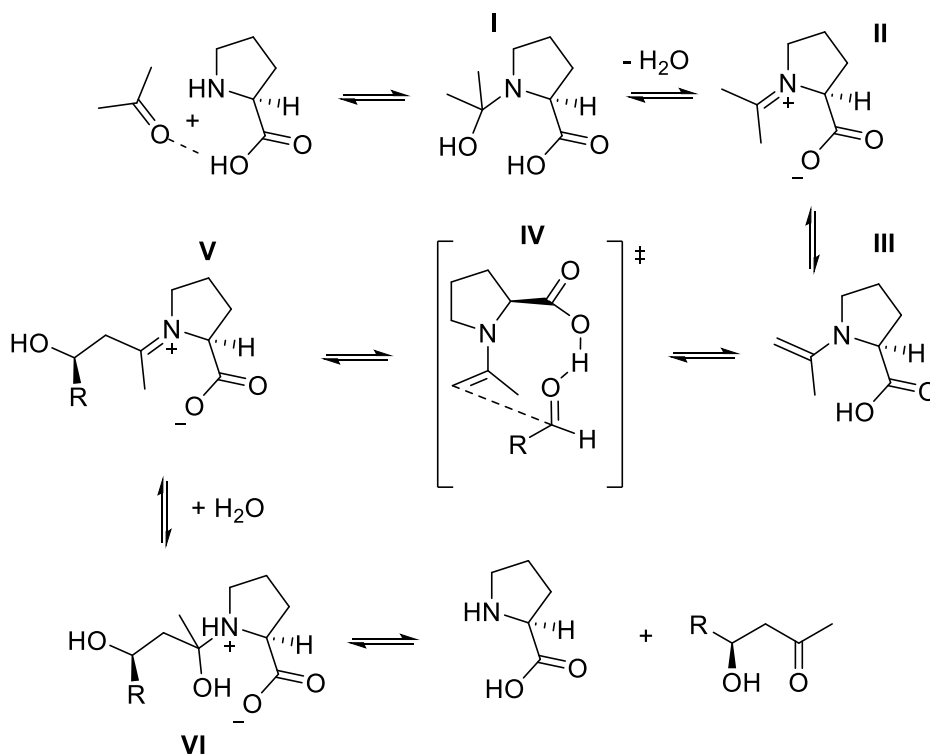
The mechanism of the reactions was not clear, therefore these chemical studies were considered unique rather than generally applicable. In the late 1990's there were only few publications that showed the use of chiral small organic molecules as catalysts, even if organocatalysis was not yet conceptualized<sup>9,10,11,12</sup>. Things started to change in 2000, when two publications, one from Barbas, Lerner and List on enamine catalysis<sup>13</sup> and the other one from MacMillan and his research group<sup>14</sup> on iminium-ion catalysis, appeared almost concurrently.

### 1.3.a. Enamine catalysis

The first example of enamine catalysis was reported by List, Barbas and Lerner<sup>13</sup>. These chemists were working on aldolase antibodies that used an enamine mechanism and they discovered that one of their catalytic antibodies was an efficient catalyst for the Hajos–Parrish–Eder–Sauer–Wiechert reaction. That was the key that allowed to establish a connection between aldolase antibodies and proline. This research was significant because it showed the use of proline as a catalyst for the direct asymmetric aldol reaction between acetone and a variety of aldehydes (Scheme 5) and also it explained, for the first time, the mechanism of the proline-catalysed reaction (Scheme 6).



**Scheme 5:** Reaction of acetone with different aldehydes under (*L*)-proline catalysis.

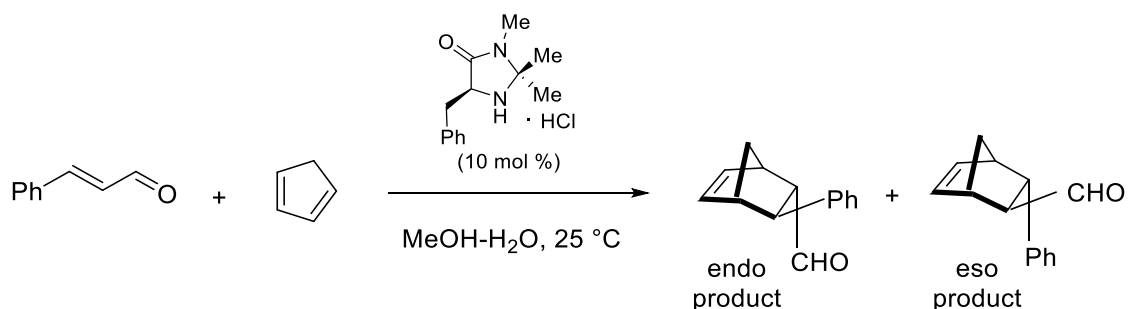


**Scheme 6:** Enamine mechanism of the proline-catalysed asymmetric aldol reaction.

In the first step of the mechanism depicted in Scheme 6, the carboxylic acid of the proline forms the carbinolamine **I**, acting as an acid catalyst. The carbinolamine **I** then undergoes dehydration to give the iminium ion **II**, which tautomerize to the correspondent enamine **III**. The enamine is a reaction intermediate, originated through reaction between a saturated carbonyl compound and a secondary amine. This intermediate possesses a carbon in  $\alpha$ -position which is more nucleophilic than the correspondent carbonyl compound and therefore, this type of activation is called *HOMO raising*. In the transition state of the reaction (**IV**) the proton of proline is shared between the carboxylate and the incoming aldehyde; in this way proline forces the addition of the aldehyde to only one of the two faces of the enamine, allowing the obtainment of an enantio-enriched product.

### 1.3.b. Iminium-ion catalysis

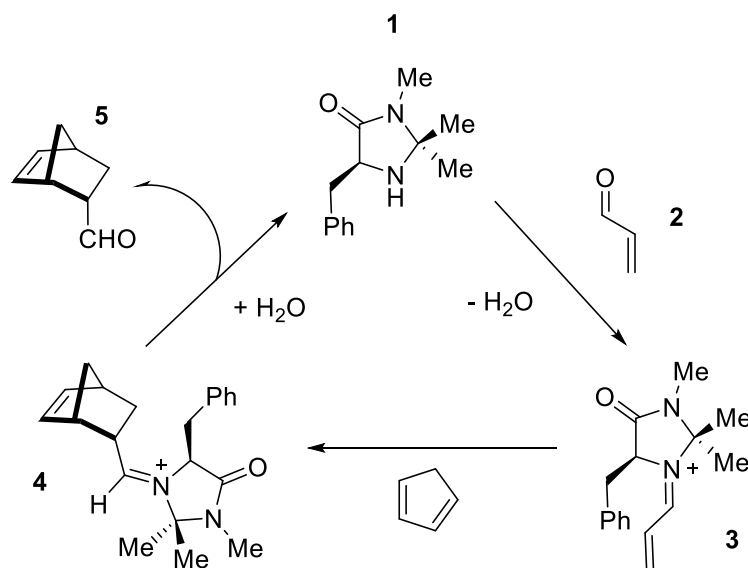
The highly enantioselective organocatalytic Diels-Alder reaction<sup>14</sup> developed by MacMillan and his group is the first example of iminium-ion catalysis (Scheme 7). Furthermore, in this work the term “organocatalysis” is introduced in the chemical literature for the first time.



**Scheme 7:** Organocatalyzed Diels-Alder reaction between cinnamaldehyde and cyclopentadiene.

Regarding the mechanism of the reaction (Scheme 8), the condensation of aldehyde **2** with an enantiopure amine **1** lead to the formation of an iminium ion **3** that is sufficiently activated to bind a diene reaction partner. The iminium ion generated possesses a carbon in  $\beta$ -position which is more electrophilic than the original aldehyde **2**, and so this type of activation is called *LUMO lowering*. In the following stages of the mechanism, Diels-Alder cycloaddition give the iminium ion **4**, which upon hydrolysis provide the enantioenriched cycloaddition product **5** and the chiral amine catalyst. The steric hindrance of the benzyl group of the catalyst forces the cycloaddition of the cyclopentadiene to only one of the two faces of the intermediate **3**, while the steric hindrance of the two methyl groups favours the trans-isomer.



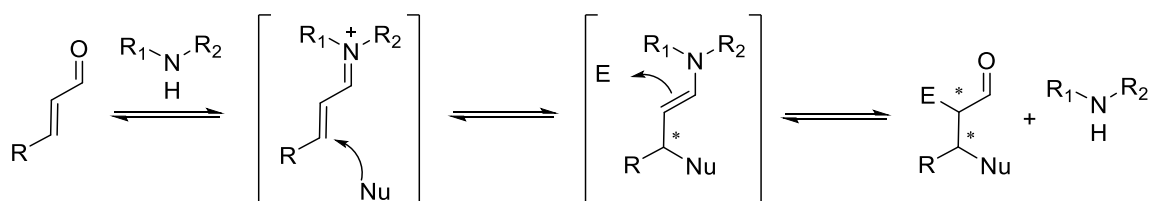


**Scheme 8:** Mechanism of enantioselective organocatalytic Diels-Alder reaction.

### 1.3.c. Tandem catalysis

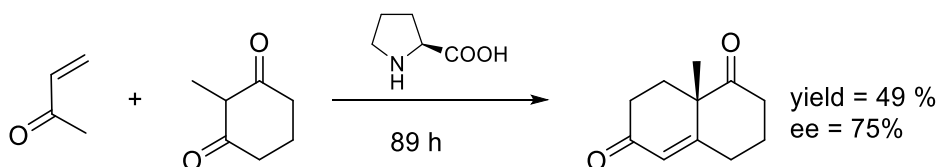
Enamine and iminium catalysis are based on the same origin, they are opposite but complementary type of catalysis, indeed List defined them as the Ying and the Yang of the organocatalysis<sup>15</sup>. For this reason, combining the two catalysis principles in tandem sequences triggered the interest of the scientific community.

As it is shown in Scheme 9, when an  $\alpha,\beta$ -unsaturated carbonyl compound reacts with a secondary amine, an iminium-ion is formed. This intermediate can therefore react with a nucleophile, forming an enamine. Subsequently the enamine reacts with an electrophile, to afford an enantio-enriched product with two stereocenters in a one-pot procedure.



**Scheme 9:** General mechanism for a tandem reaction.

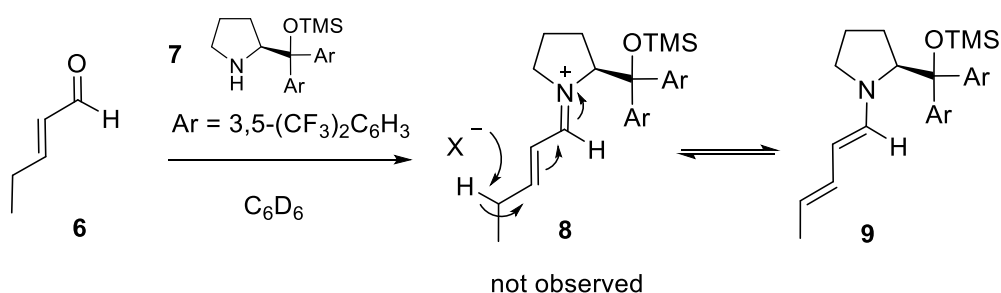
In 2000, Barbas and Bui reported for the first time an example of tandem catalysis<sup>16</sup>: a single-step enantioselective Robinson annulation reaction catalysed by (*L*)-proline and other chiral amines, depicted in Scheme 10.



**Scheme 10:** Single-step asymmetric Robinson annulation.

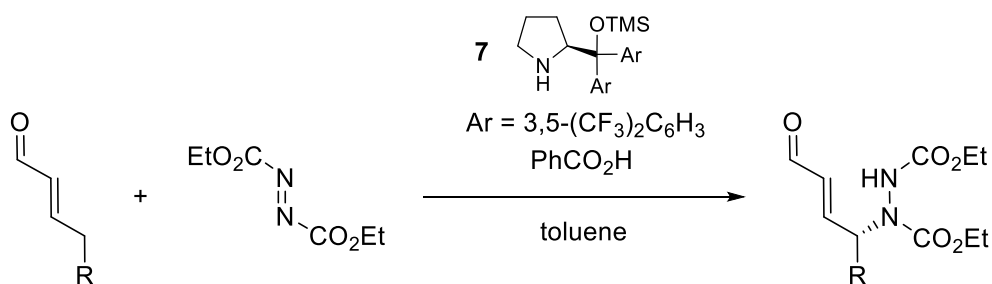
### 1.3.d. Dienamine catalysis

In 2006, another type of organocatalysis (dienamine catalysis) was introduced by Jørgensen and his co-workers<sup>17</sup>. This research group conducted <sup>1</sup>H-NMR spectroscopic investigations to verify the presence of the expected iminium-ion intermediate (**8**), formed by reaction between 2-pentenal (**6**) and the chiral catalyst **7**. Surprisingly, they observed that the majority of the catalyst was present in the form of the dienamine **9** (Scheme 11).



**Scheme 11:** Formation of the dienamine intermediate in the reaction between 2-pentenal and the chiral catalyst.

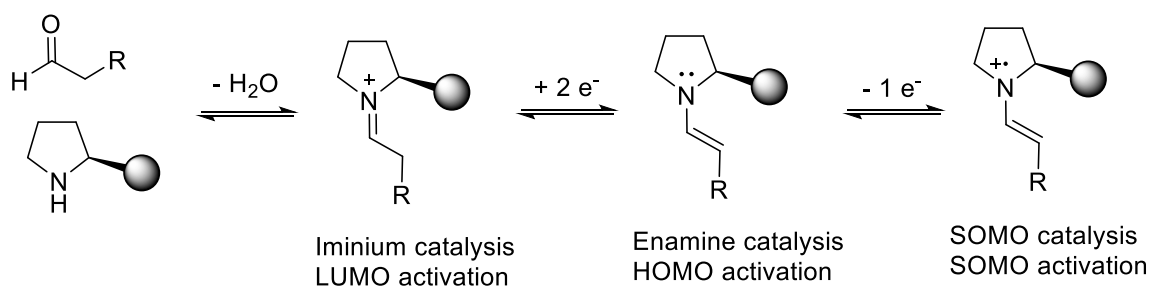
As a matter of fact, the counterion of the iminium-ion removes the proton in  $\gamma$ -position, forming the dienamine. In this way, the  $\gamma$ -position becomes nucleophilic. Besides, to explore the potential on the discovery of the dienamine intermediate, Jørgensen and his collaborators performed experiments to investigate the ability to  $\gamma$ -functionalize aldehydes. As a consequence, a new protocol for the  $\gamma$ -amination of  $\alpha,\beta$ -unsaturated aldehydes using 2-[bis(3,5-bistrifluoromethylphenyl)-trimethyl-silyloxymethyl]-pyrrolidine **7** as the catalyst was discovered (Scheme 12).



**Scheme 12:**  $\gamma$ -Amination of  $\alpha,\beta$ -unsaturated aldehydes.

### 1.3.e. SOMO catalysis

SOMO catalysis was introduced for the first time by McMillan in 2007<sup>18</sup>. In this activation strategy a one electron oxidation of an enamine intermediate generate a 3- $\pi$ -electrons radical cation with a singly occupied molecular orbital (SOMO) (Fig. 4).



**Fig. 4:** General comparison between the different activation strategies discussed.

The novelty of this type of activation resides in the fact that the radical generated possesses a carbon in  $\alpha$ -position which is electrophilic. As a consequence, carbonyl compounds can be  $\alpha$ -functionalized through reaction with nucleophilic reagents.

### 1.3.f. Advantages and limits of organocatalysis

Once the field of organocatalysis had been defined, it grew quickly, mainly thanks to its advantages. Indeed, small organic molecules are generally insensitive to oxygen and moisture in the atmosphere, they are typically non-toxic and environmentally friendly, increasing the safety of catalysis. Moreover, a

wide range of organic enantiopure reagents are naturally available from biological sources and these catalysts are therefore cheap to prepare and accessible in a range of quantities. In contrast, metal-based catalysts are usually more toxic, expensive and sensitive to air and moisture than organocatalysts.

Regarding the drawbacks of organocatalysis, the low turnover numbers might limit the potential uses of organocatalysis for industrial applications and also the catalytic loading is usually high (from 2% M to 20% M)<sup>5</sup>. All in all, thanks to its numerous advantages, enantioselective organocatalysis has emerged as a powerful synthetic way for the development of new methods to synthesize diverse chiral molecules.

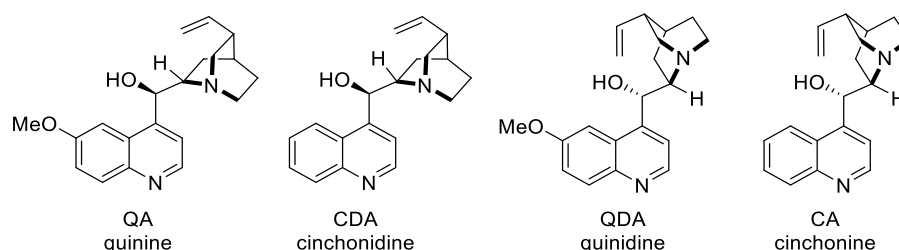
#### **1.4. BIFUNCTIONAL ORGANOCATALYSIS**

Bifunctional catalysis concerns the use of low molecular weight molecules possessing two distinct functional groups: in general a Lewis or Brønsted basic functionality (a tertiary amine) and a hydrogen-bond donor group (an acidic portion) positioned over a chiral scaffold. These functional groups act in catalysis not independently but cooperatively; indeed, they activate the reacting molecules simultaneously<sup>19</sup>. Importantly, these acidic moieties act as “neutral” hydrogen-bond donors, because they do not quench the basic functionality by quantitative protonation. Even in nature, enzymes similar to aldolase of type II form an enolate through hydrogen bonds interactions with carbonyl donor, followed by deprotonation with a weak base<sup>20</sup>.

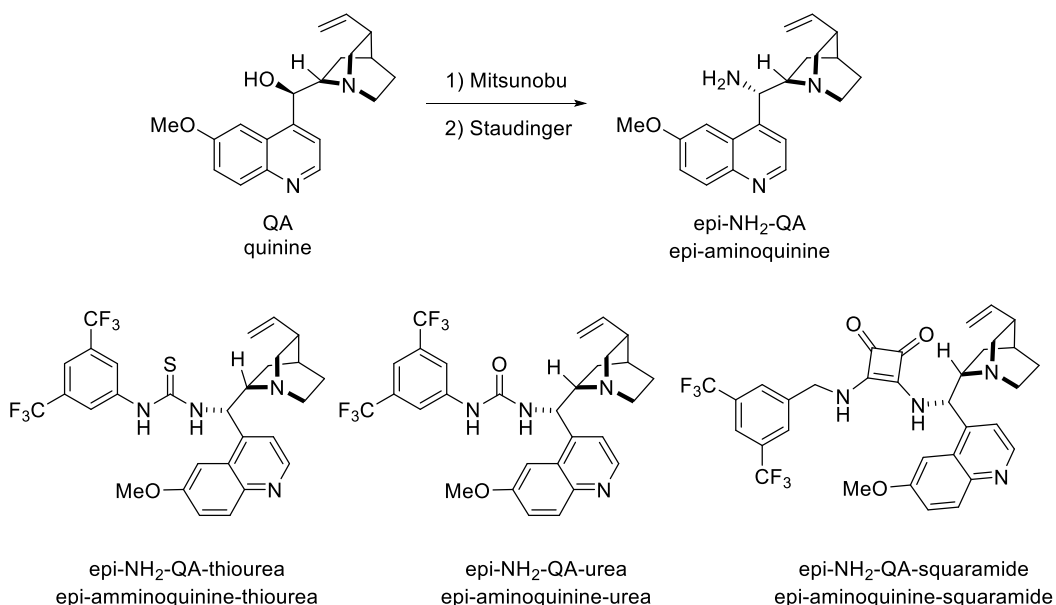
##### **1.4.a. Cinchona alkaloids**

An important class of bifunctional catalyst is represented by the cinchona alkaloids (Fig. 5). The natural Cinchonas are bifunctional catalyst themselves, but they can be transformed into their epi-amino derivatives through Mitsunobu reaction. In addition, simple condensation of the epi-amino derivatives with isothiocyanates and isocyanate renders the corresponding thioureas and ureas

(Fig. 6). Besides, it is important to underline that quinine and quinidine are diastereoisomers that behave as enantiomeric catalysts even if they are not enantiomer. They are defined as pseudo-enantiomeric pairs and the same concept is therefore valid for cinchonidine and cinchonine.



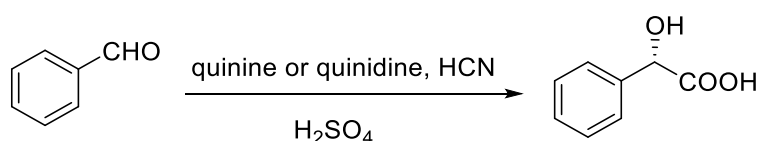
**Fig. 5:** Natural cinchona alkaloids.



**Fig. 6:** *Epi*-amino derivatives of natural cinchona alkaloids.

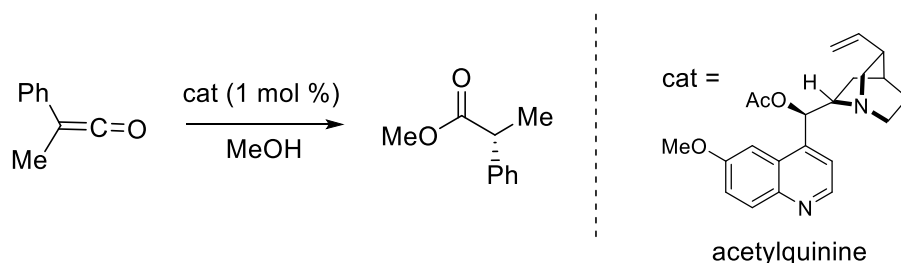
Cinchona alkaloids are isolated from the bark of several species of cinchona trees and they were firstly launched in the European market in the early seventeenth century, after the discovery of the antimalarian property of cinchona bark<sup>19</sup>. In 1820, Pierre-Joseph Pelletier and Bienaimè Caventou isolated for the first time quinine, the active compound of the bark and since then cinchona alkaloids have played an important role in medicine. The first use of cinchona alkaloids in organic chemistry was discovered by Pasteur in 1853 who exploited

the potential of these alkaloids as resolving agents<sup>21</sup>. However, one of the most relevant application of cinchona alkaloids in chemistry resides in their ability to promote different enantioselective transformations. The first use of a cinchona alkaloid as a catalyst for asymmetric reaction was published in 1912 by Breiding and Fiske<sup>22</sup> (Scheme 13). They observed that quinine and quinidine accelerated the addition of HCN to benzaldehyde and that the resulting cyanohydrins were optically active and are of opposite chirality. However, the enantiomeric excesses were very low, reaching a maximum of 9 %.



**Scheme 13:** Enantioselective addition of HCN to benzaldehyde.

In 1960, Pracejus studied the addition of methanol to phenylmethylketene using O-acetylquinine as catalyst (Scheme 14) to afford  $\alpha$ -phenyl methylpropionate<sup>23</sup>. He obtained, for the first time, useful levels of enantioselectivity (74 % ee), using a derivate of a natural cinchona alkaloid.



**Scheme 14:** Enantioselective addition of methanol to phenylmethylketene.

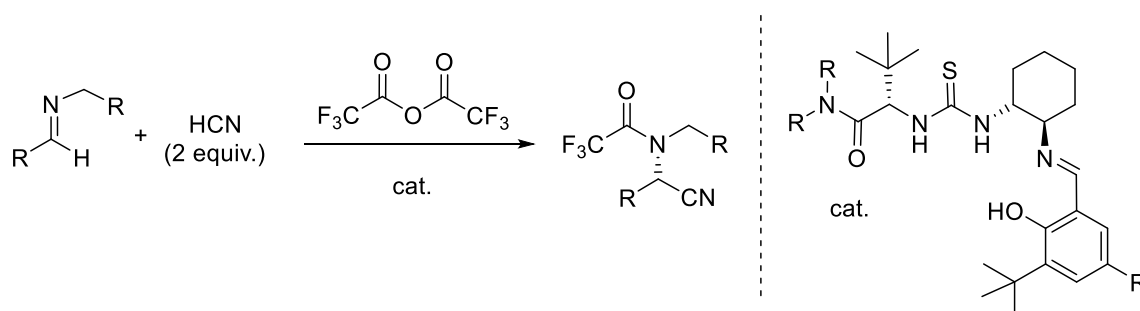
Things significantly change in the late 1980's, when Wynberg and his co-workers launched a new era in the asymmetric catalysis driven by cinchona alkaloids. In their studies<sup>24</sup> they demonstrated that this class of alkaloids could be highly versatile catalysts for a wide range of enantioselective transformations like the addition of ketenes to carbonyl compounds, resulting in  $\beta$ -lactones. Since their studies, the use of cinchona alkaloids as asymmetric catalyst significantly increased and nowadays, cinchona alkaloids and their derivatives are considered one of the most "privileged" chiral catalyst<sup>25</sup>, indeed they demonstrate highly levels of enantioselectivity for a broad range of substrates.

In particular, the bulky and highly basic quinuclidine is primary responsible for the catalytic activity of this alkaloids, indeed this moiety makes this alkaloids efficient ligand for a variety of metal-catalysed processes. Moreover, the quinuclidine nitrogen can be used as a chiral base or as a chiral nucleophilic catalyst, promoting a great majority of organocatalytic reactions. On the other hand, the secondary 9-hydroxy group can work as an acid site or as hydrogen bond donor and his derivatization into ureas, amides, and thioureas, provides more powerful acidic sites or hydrogen bond donors. The 6 *o*-methoxy group of quinine and quinidine can also be transformed into a free OH group or into a thiourea moiety, which can work as an effective H-bond donor.

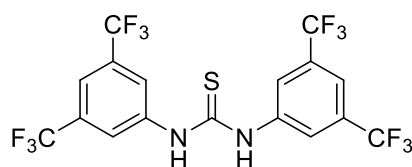
#### 1.4.b. Thiourea organoderivatives

Thiourea derivatives represent an important class of “privileged” organocatalysts. Certainly, their catalytic activity is associated with the ability to form hydrogen bonds with substrates. Moreover, multiple hydrogen-bonding interactions can also significantly stabilize anionic species and transition states involved in the reaction, allowing kinetically more convenient pathways<sup>26</sup>.

In 1998 Jacobsen demonstrated that thiourea organoderivatives were able to catalyse the Strecker reaction in an asymmetric fashion (Scheme 15), proving that the weak hydrogen-bonding interactions can promote organic reactions<sup>27</sup>.



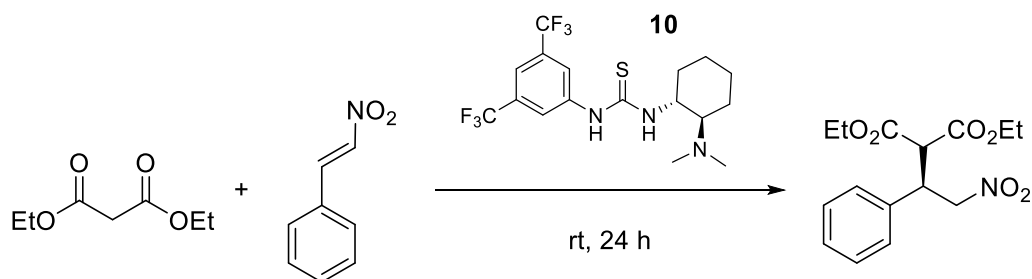
**Scheme 15:** Asymmetric Strecker reaction.



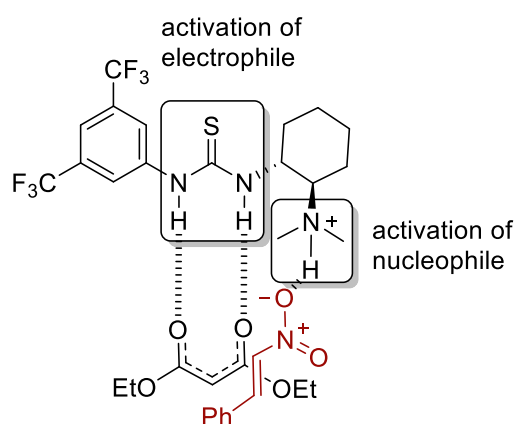
**Fig. 7:** N,N'-bis[3,5-bis(CF<sub>3</sub>)-phenyl]thiourea.

One of the first prototype of thiourea organocatalyst was introduced by Wittkopp and Schreiner in 2002<sup>28</sup>. Their studies on Dienes-Alder reaction catalysed by N,N'-bis[3,5-bis(CF<sub>3</sub>)-phenyl]thiourea (Fig. 7) highlighted the potential of thiourea-catalysis and, subsequently, the combination of thioureas with various amines in a chiral scaffold led to the development of bifunctional organocatalyst.

Indeed, in 2003, Takemoto and his collaborators reported the addition of malonates to nitroalkenes, catalysed by the chiral thiourea **10** also known as Takemoto Catalyst<sup>29</sup> (Scheme 16).



**Scheme 16:** Enantioselective addition of malonates to nitroalkenes.



**Fig. 8:** Activation strategy of the Takemoto catalyst.

In this type of reaction, the basic chiral tertiary amine removes the proton of the nucleophile. Subsequently, the proton removed coordinates the oxygen of the

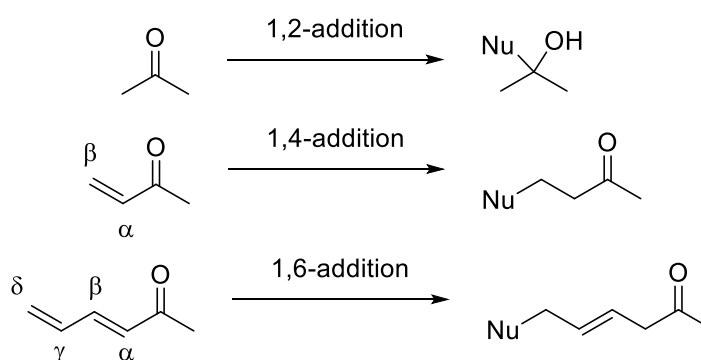


nitroalkene. In the meantime, the malonate is activated by the acidic hydrogens of the thiourea (*LUMO activation*) (Fig. 8).

## 1.5. VINYLOGY

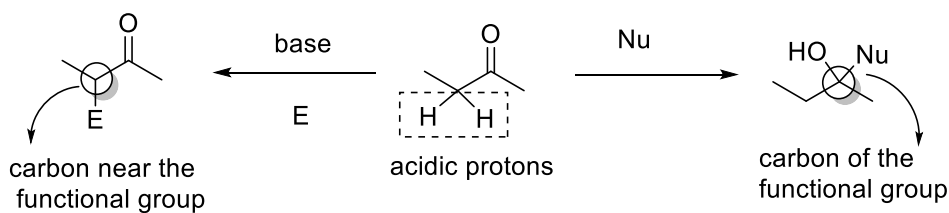
Vinylogy was introduced in 1935 by Fuson<sup>30</sup> to explain the unusual reactivity of  $\alpha,\beta$ -unsaturated carbonyl compounds. He stated that “in a molecule containing a system of conjugated double linkages, the influence of a functional group may sometimes be propagated along the chain and make itself apparent at a remote point in the molecule”.

Taking into account nucleophilic additions (Fig. 9), the Michael addition (1,4-addition) can be considered as the vinylogous correspondent of the direct addition to the carbonyl, indeed the electronic effect of the carbonyl is propagated through the conjugated double bond.



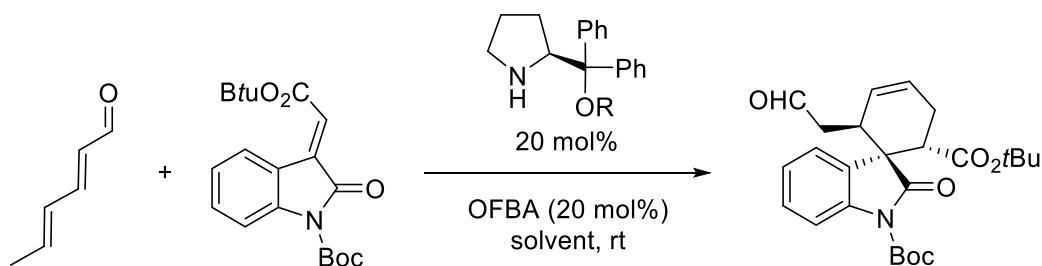
**Fig. 9:** Vinylogy in nucleophilic addition.

Even if the formation of carbon-carbon bond has represented an interesting challenge in organic chemistry, often this functionalization is limited to the carbon of the functional group or the one adjacent to it (Scheme 17). On the other hand, through vinylogous reactions, it is possible to functionalize carbon which are in positions that are far away from the functional groups.

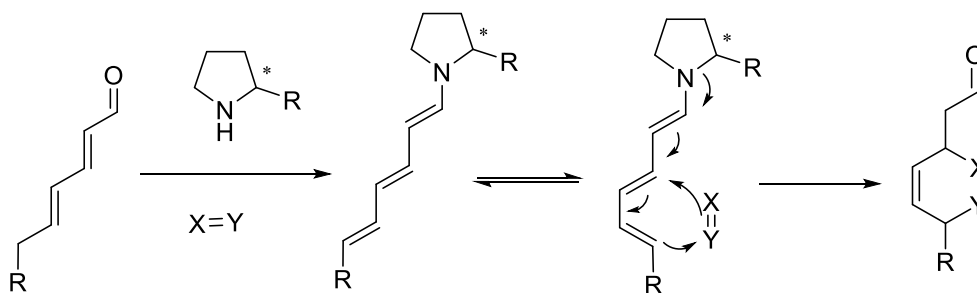


**Scheme 17:** Classical strategies to create a carbon-carbon bond.

The reactivity in  $\gamma$  position was previously introduced in the dienamine catalysis. Similarly to the dienamine catalysis, trienamine catalysis allows the functionalization of the  $\epsilon$  position. Among the numerous examples of vinylogous reactions, it is worth mentioning the one reported by Jørgensen and his co-workers in 2001<sup>31</sup> (Scheme 18).



**Scheme 18:** Diels-Alder Reaction of 2,4-Hexadienal with 3-Olefinicoxindole.

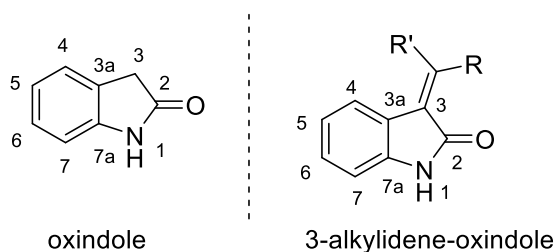


**Scheme 19:** HOMO activation through trienamine catalysis.

In their work they proposed for the first time a Diels-Alder reaction to form a spiro-compound with numerous stereocenter, employing the formation of a trienamine intermediate (Scheme 19).

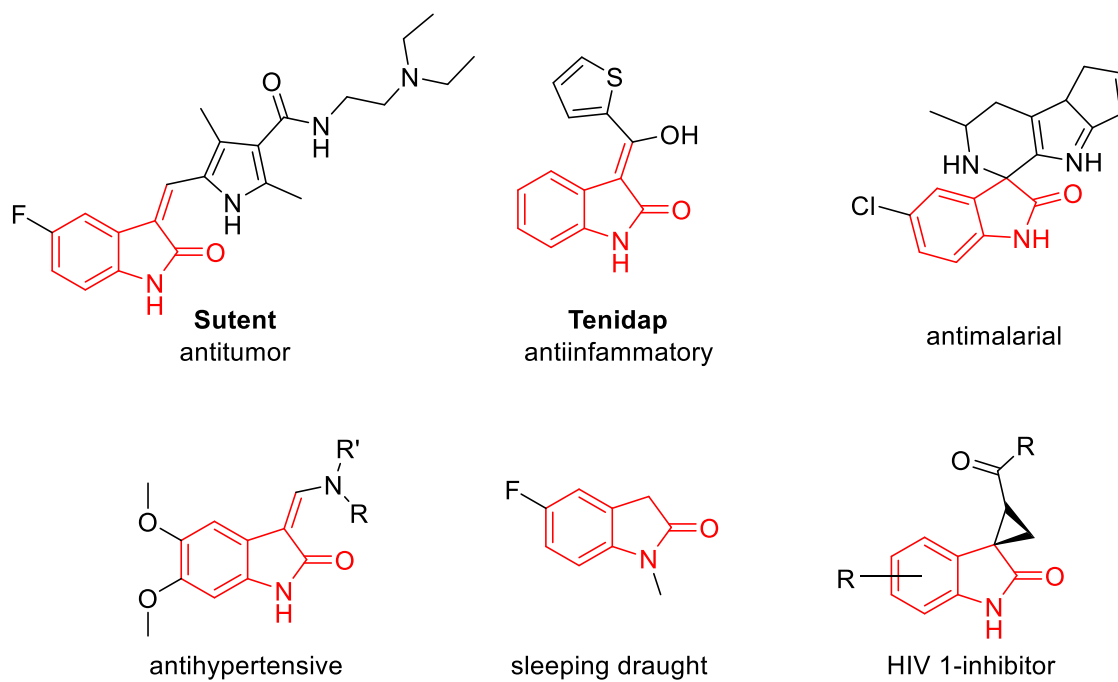
## 1.6. THE SUBSTRATES: OXINDOLES AND 3-ALKYLIDENE OXINDOLES

Throughout the years, oxindoles and his derivatives have received much attention as synthetic intermediates for the synthesis of biologically active compound<sup>32</sup>. Certainly, oxindole is a presumed tryptophan metabolite, normally metabolized and detoxified from the body to the liver and chemicals from this class are known to possess sedative and antioxidant effects. The structure of the oxindole consists of a six-membered benzene ring fused to a five-membered nitrogen-containing ring. On the other hand, 3-alkylidene oxindole differs from oxindole only for a double carbon-carbon bond in position 3 (Fig. 10).



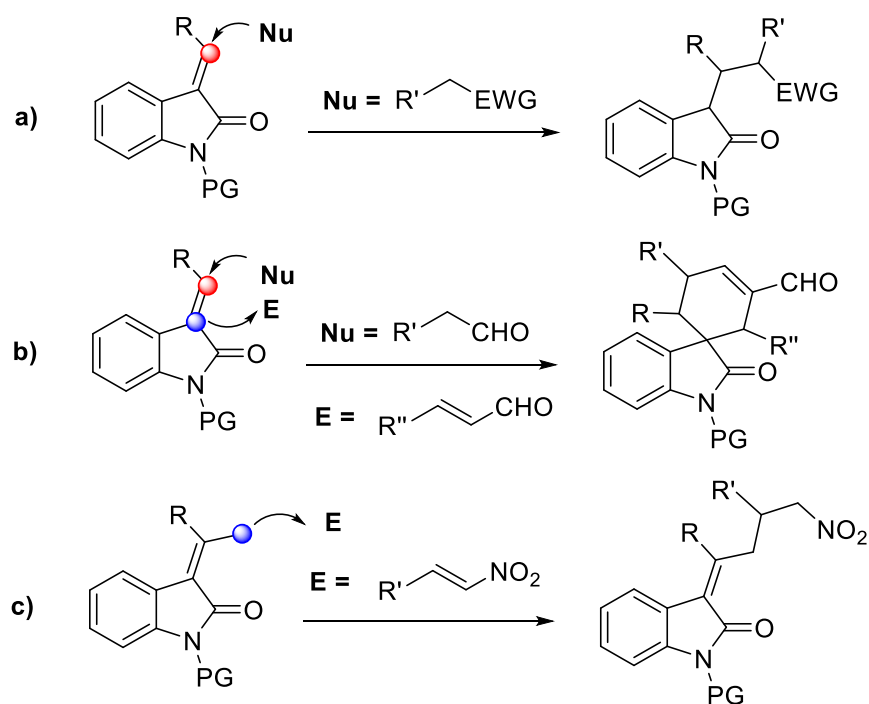
**Fig. 10:** Structures of the oxindole and the 3-alkylidene oxindole.

3-Alkylidene oxindoles are, indeed, considered attractive compounds for the discovery of new biologically active molecules, and today several compounds containing this moiety, are currently employed in treatment of various diseases<sup>33,34</sup> (Fig. 11). For instance, the discovery of SU11248, marketed as Sutent<sup>TM</sup>, published and patented by Sugen/Pharmacia then approved by the United States' Food and Drug Administration (US FDA) in 2006, represented a turning point in the treatment of gastrointestinal stromal tumors and advanced renal cell carcinoma<sup>35</sup>.



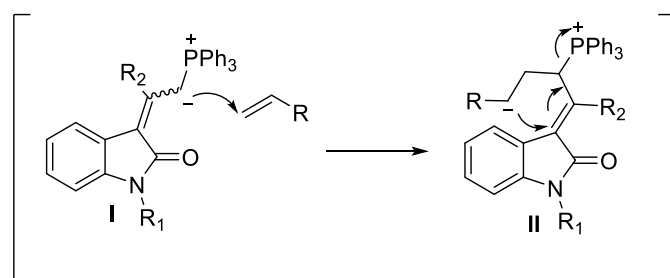
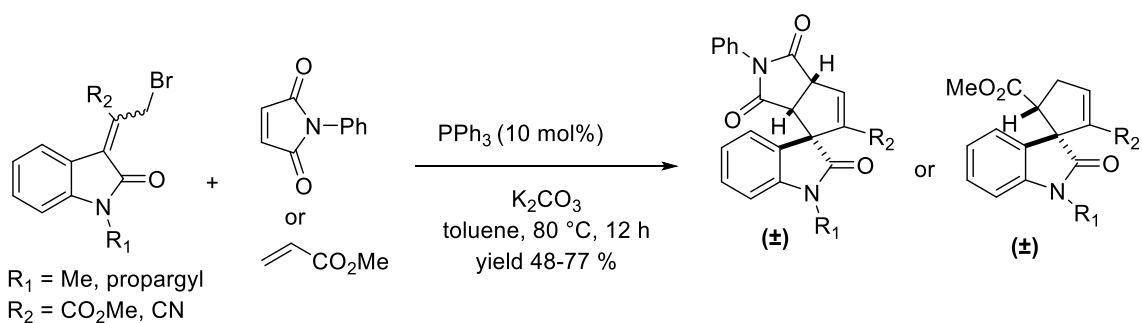
**Fig. 11:** Active compounds of different drugs where the oxindole core is red-coloured.

Regarding the reactivity of 3-alkylideneoxindoles; the pro-chiral electrophilic character was widely exploited for the asymmetric synthesis of oxindoles and spirooxindoles<sup>36</sup>, where the 3-alkylideneoxindoles can be considered as Michael acceptors and can therefore react with carbanions to afford  $\beta$ -substituted-3-alkylideneoxindoles (Scheme 20 a e b).



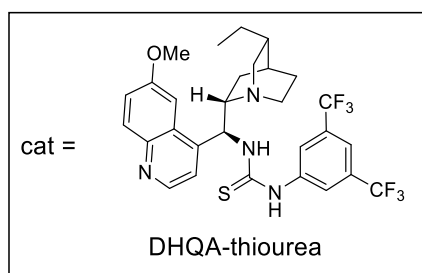
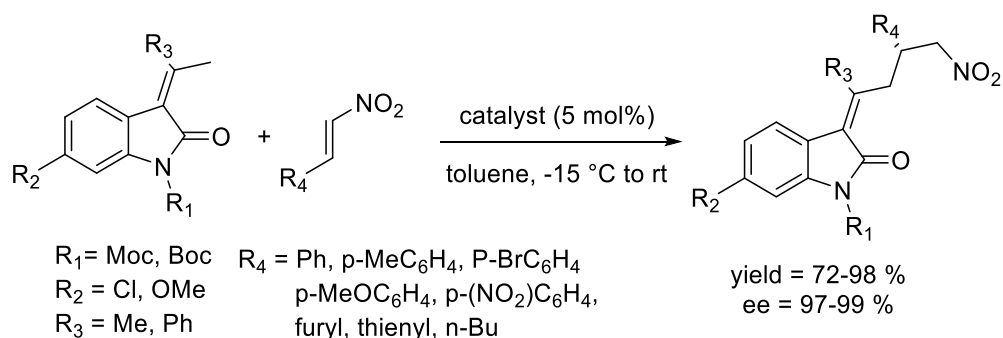
**Scheme 20:** Reactivity of 3-alkylidene oxindoles. The nucleophilic site is indicated in blue, while the carbon electrophile is highlighted in red.

However, the vinylogous pro-nucleophilic character of the alkyl group attached at the  $\beta$ -position of the ylidene has been explored only in recent years (Scheme 20 c)<sup>37</sup>. Indeed, in 2010, Shanmugam and co-workers reported the first diastereoselective direct Michael addition in which 3-alkylidene-oxindoles were employed as vinylogous nucleophiles (Scheme 21)<sup>38</sup>. In their work they performed a [3+2]-cycloaddition reaction between 3-alkylidene oxindoles and Michael acceptors such as N-phenyl maleimide and methyl acrylate to obtain 3-spirocyclopentene-2-oxindoles. The reaction is promoted by  $\text{PPh}_3$ , which is able to form, in the presence of a base, the ylide **I**. Afterwards, as illustrated in scheme 20, the ylide **II** undergoes vinylogous Michael addition to the acceptor.

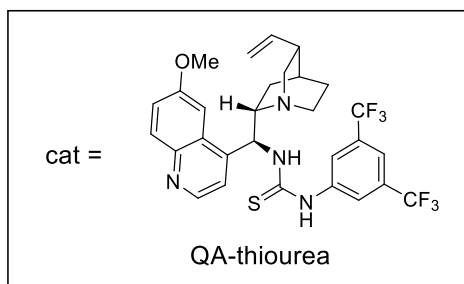
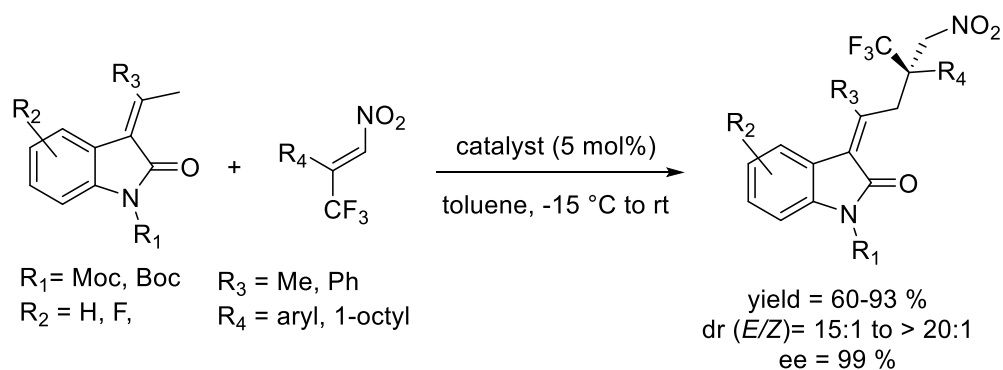


**Scheme 21:** Enantioselective synthesis of 3-spirocyclopentene-2-oxindoles through [3+2]-cycloaddition reaction.

Two years later, in 2012, Curti, Casiraghi and collaborators disclosed the first example of an organocatalysed direct enantioselective vinylogous Michael addition of 3-alkylidene oxindoles to nitroolefines<sup>39</sup> (Scheme 22) to afford  $\gamma$ -substituted 3-alkylidene oxindoles with good levels of regio-, diastereo- and enantioselectivity. In contrast to the publication of Shanmugan, in this case, the enantioselective version of the reaction was the focus of the work. The bifunctional catalysis resulted fundamental for the enantiocontrol of the reaction: the basic functionality of the catalyst forms the dienolate of the 3-alkylidene oxindoles, while the acidic functionality is responsible for the activation of the nitroolefine. Moreover, the insertion of electron-withdrawing groups like Moc or Boc at the indole nitrogen atom turned out to be essential for the success of the reaction. Furthermore, Wang and co-workers<sup>40</sup>, in 2014, described an enantioselective vinylogous addition of 3-alkylidene oxindoles to  $\beta,\beta$ -disubstituted nitroolefines to afford oxindoles derivatives containing a trifluoromethylated carbon stereocenter (Scheme 23). The reaction was catalysed by the bifunctional quinine derivative catalyst.

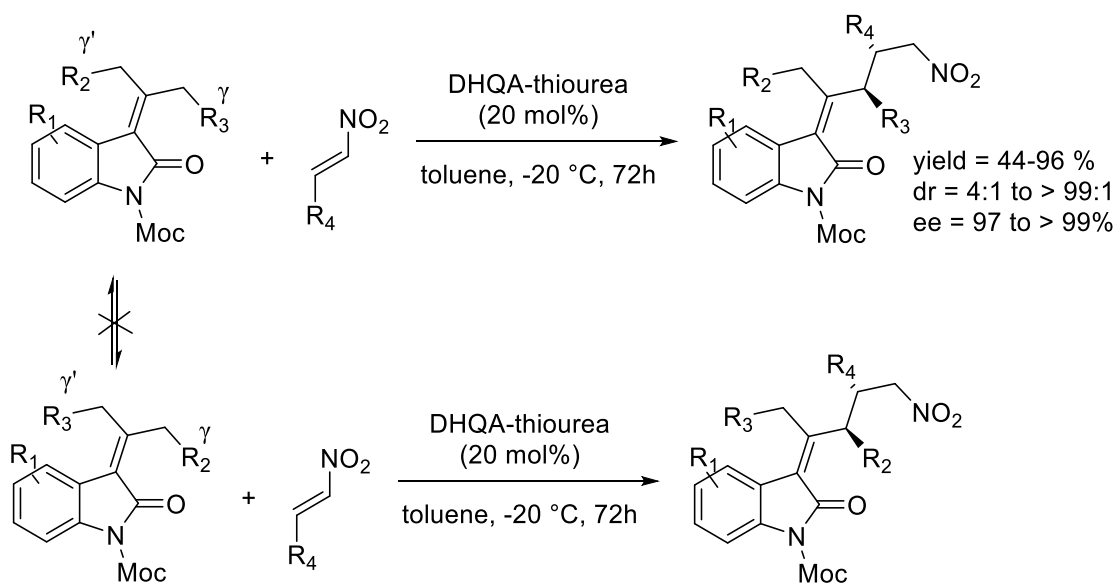


**Scheme 22:** Enantioselective Vinylogous Michael addition of 3-alkylidene oxindoles to nitroolefines.



**Scheme 23:** Enantioselective vinylogous addition of 3-alkylidene oxindoles to  $\beta,\beta$ -disubstituted nitroolefines.

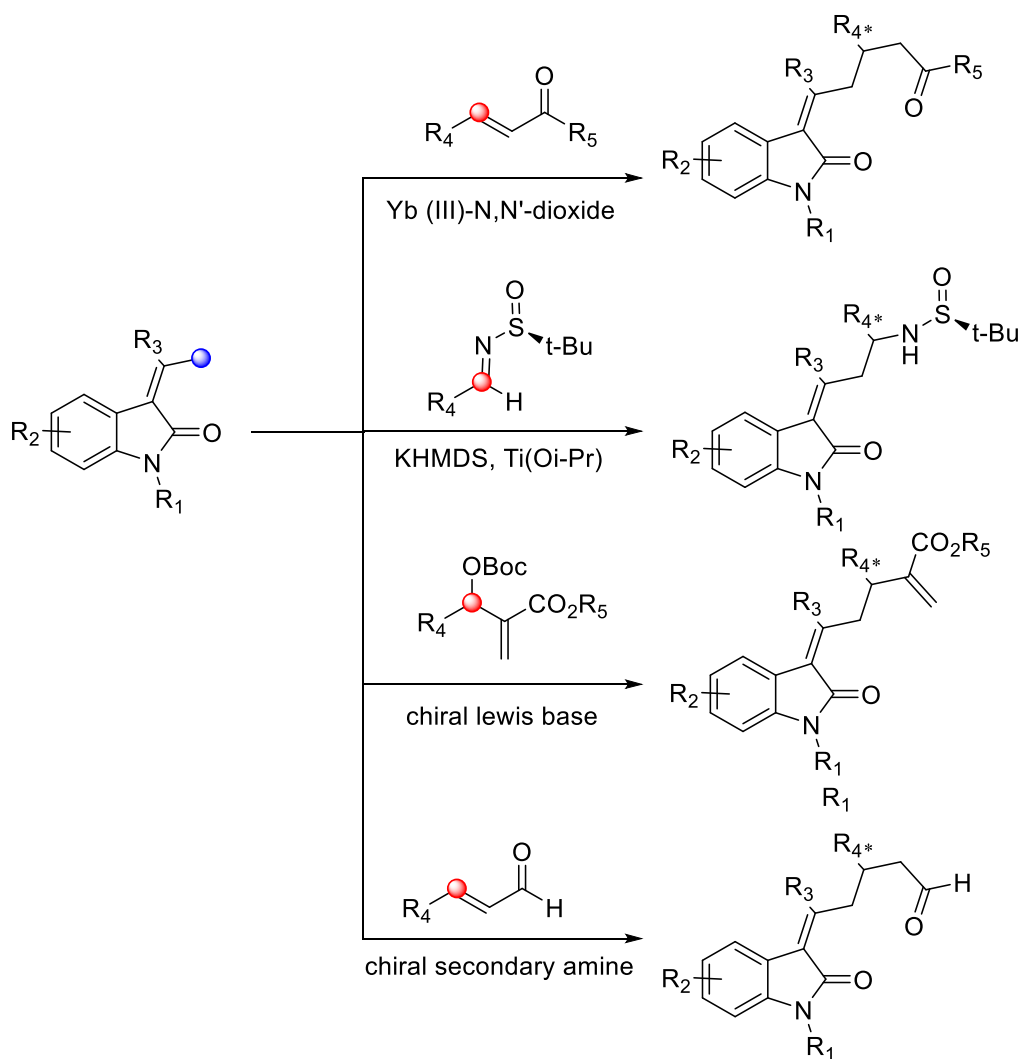
Another example of vinylogous Michael addition between 3-alkylidene oxindoles and nitroolefines was reported by our research group in 2015<sup>41</sup> (Scheme 24). Unlike the work of Curti and Casiraghi, this time the use of oxindoles bearing nonsymmetric 3-alkylidene groups was the focal point of the paper.



**Scheme 24:** Organocatalytic vinylogous Michael addition of non-symmetric 3-alkylidene oxindoles to nitroalkenes.

In this work, the reaction is performed at  $-20\text{ }^\circ\text{C}$  to inhibit the interconversion between the two (*E*)/(*Z*) isomers of the 3-alkylidene oxindole and to obtain  $\gamma$ -substituted 3-alkylidene oxindoles with good levels of regio-, diastereo- and enantioselectivity. It was demonstrated that the reaction proceeded only via a  $\gamma$ -site selective deprotonation, which is the rate-determining step. Besides, the catalyst deprotonates only the  $\gamma$ -position and exclusively interacts with the nitroalkene, through hydrogen bonding. In the meantime, several cases employing the 3-alkylidene oxindoles as nucleophiles in the vinylogous reactions have been reported, employing as acceptors enones<sup>42</sup>, imines<sup>43</sup>, MBH carbonate<sup>44</sup> and  $\alpha,\beta$ -unsaturated aldehydes<sup>45</sup> (illustrated in order in Scheme 25).

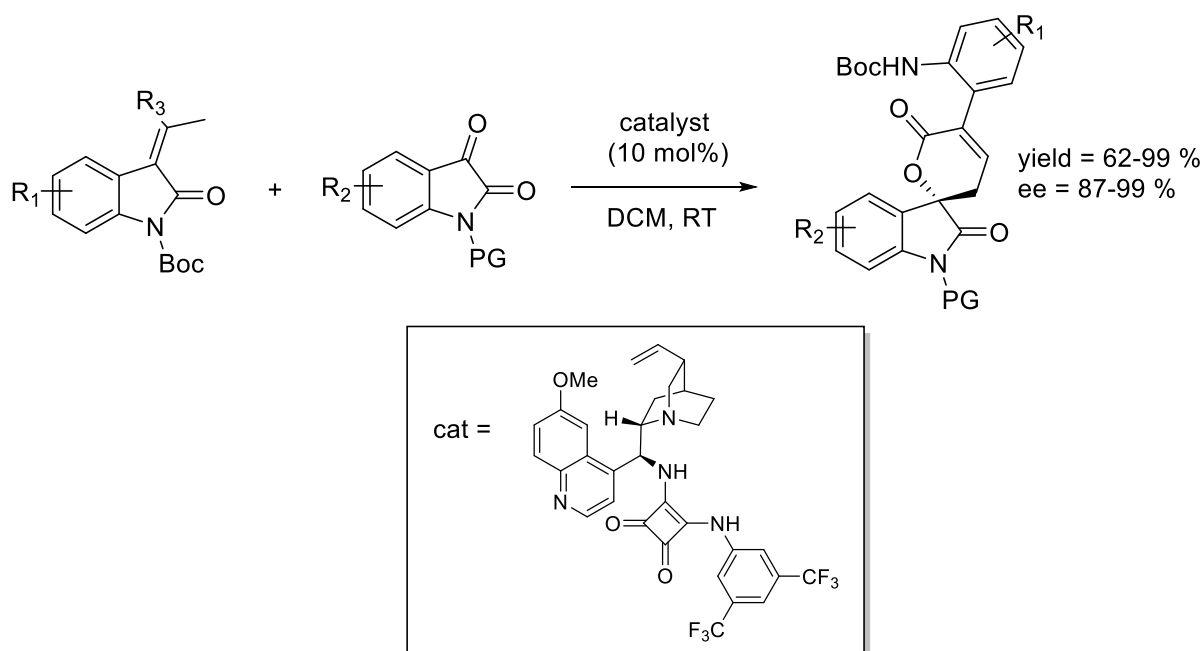




**Scheme 25:** Different acceptors employed in vinylogous reaction with 3-alkylidene oxindoles.

The enolizable site is indicated in blue, while the carbon electrophile is highlighted in red.

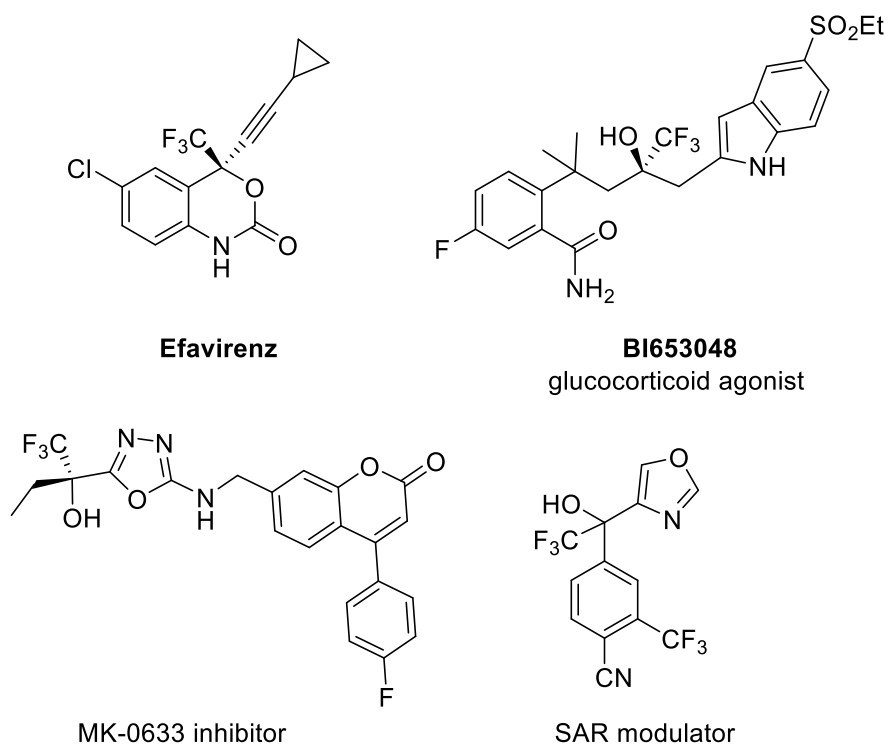
Moreover, it is worth mentioning the enantioselective organocatalytic vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles to isatins developed by Han and Chang in 2016<sup>46</sup> (Scheme 26). This work represents the only example in which the initial aldol reaction is followed by an unexpected intramolecular lactonization, leading to the generation of spirooxindole dihydropyranones in good to excellent yields with high enantioselectivities.



**Scheme 26:** Enantioselective organocatalytic vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles to isatins.

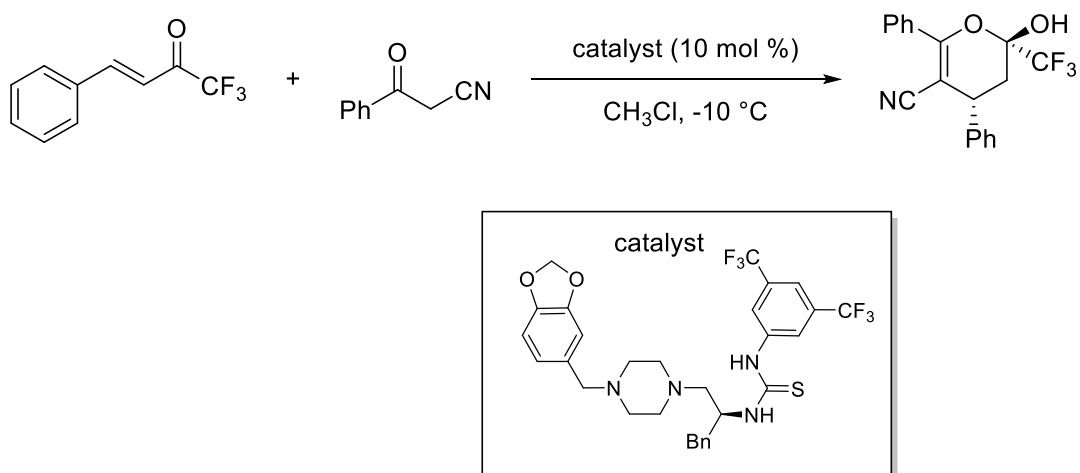
### 1.7. THE SUBSTRATES: $\alpha,\beta$ -UNSATURATED TRIFLUOROMETHYL KETONES

Since its versatility, the reactivity of  $\alpha,\beta$ -unsaturated trifluoromethyl ketones has been exploited in numerous asymmetric transformations, including hydrogenation<sup>47</sup>, aldol<sup>48</sup>, epoxidation<sup>49</sup>, Michael-type<sup>50</sup>, and Diels–Alder<sup>51</sup> reactions in order to afford chiral trifluoromethylated organic compounds. In particular, the aldol reaction provides an efficient and convenient access to chiral trifluoromethylated tetrasubstituted carbon centers<sup>52</sup>. Indeed, since organic molecules containing a trifluoromethyl moiety possess unique physical and biological properties, the demand for reliable methods for their enantioselective synthesis has increased<sup>53</sup>. As a matter of fact, for the interesting characteristic of the fluorine atom, early one-third of all the substances present on the pharmaceutical and agrochemical market contain fluorine atom<sup>54</sup> and among them there are many trifluoromethylated compounds. Relevant examples are the anti-HIV drug Efavirenz and glucocorticoid agonist BI653048<sup>55</sup>, used for the treatment of rheumatoid arthritis (Fig. 12).



**Fig. 12:** Biologically active trifluoromethylated compounds.

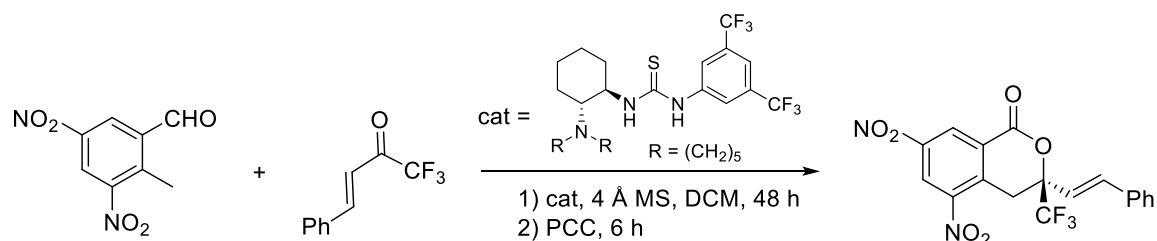
An example of organocatalytic asymmetric reaction of electron-deficient  $\alpha,\beta$ -unsaturated trifluoromethyl compound was described, in 2009, Zhu and collaborators<sup>56</sup> (Scheme 27).



**Scheme 27:** Enantioselective Michael addition of  $\alpha$ -cyanoketones to  $\alpha,\beta$ -unsaturated trifluoromethyl ketones.

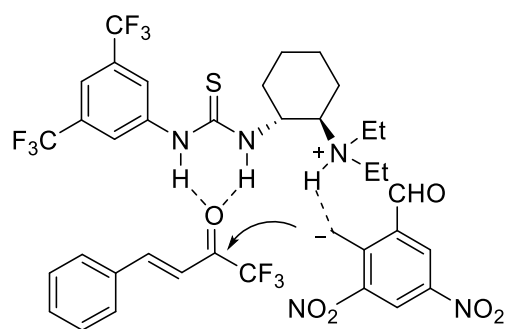
They performed the first enantioselective Michael addition of  $\alpha$ -cyanoketones to  $\alpha,\beta$ -unsaturated trifluoromethyl ketones, followed by hemiacetalization using a bifunctional thiourea catalyst. The reaction allowed the obtainment of trifluoromethyl dihydropyrans in high yields and ee higher than 95%.

On the other hand, one recent relevant example of addition to trifluoromethyl ketones has been reported by Li and his co-workers<sup>57</sup> (Scheme 28).



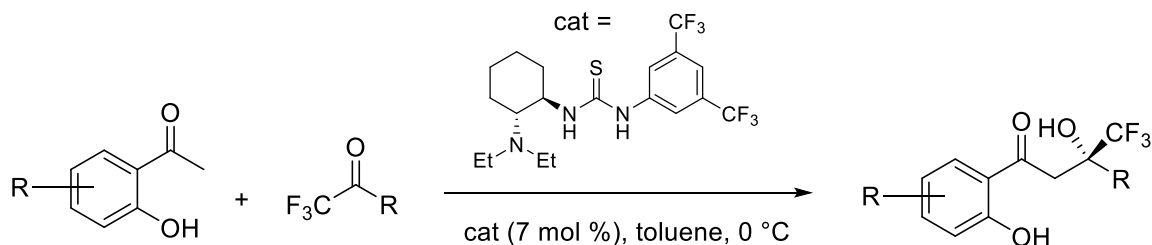
**Scheme 28:** Enantioselective benzylation and aldol-hemiacetalization between 2-methyl-3,5-dinitrobenzaldehyde and  $\alpha,\beta$ -unsaturated trifluoromethyl ketones.

They performed an asymmetric benzylation and aldol-hemiacetalization between 2-methyl-3,5-dinitrobenzaldehyde and  $\alpha,\beta$ -unsaturated trifluoromethyl ketones to provide enantioselective access to 3,4-dihydroisocoumarin derivatives with a trifluoromethylated tetrasubstituted carbon stereocenter. The reaction is catalysed by a chiral bifunctional thiourea. According to the mechanism proposed by Li and his collaborators (Fig. 13), the chiral centre is created during the asymmetric aldol reaction, in which the nucleophile is activated by the tertiary amine and the ketone is activated by hydrogen bonding interactions with the thiourea. Subsequently, the benzylic anion derived from 2-methyl-3,5-dinitrobenzaldehyde attack the carbonyl of the trifluoromethyl ketone from the *Re* face, forming an (*S*)-configured aldol product. Then, through intramolecular hemiacetalization followed by oxidation, it is possible to afford the correspondent 3,4-dihydroisocoumarin derivative.



**Fig. 13:** Proposed transition state model.

Furthermore, it is worth mentioning also the cross-aldol reaction of *o*-hydroxyacetophenones and trifluoromethyl ketones catalyzed by chiral thioureas reported in this year by Da and his collaborators<sup>58</sup> (Scheme 29).

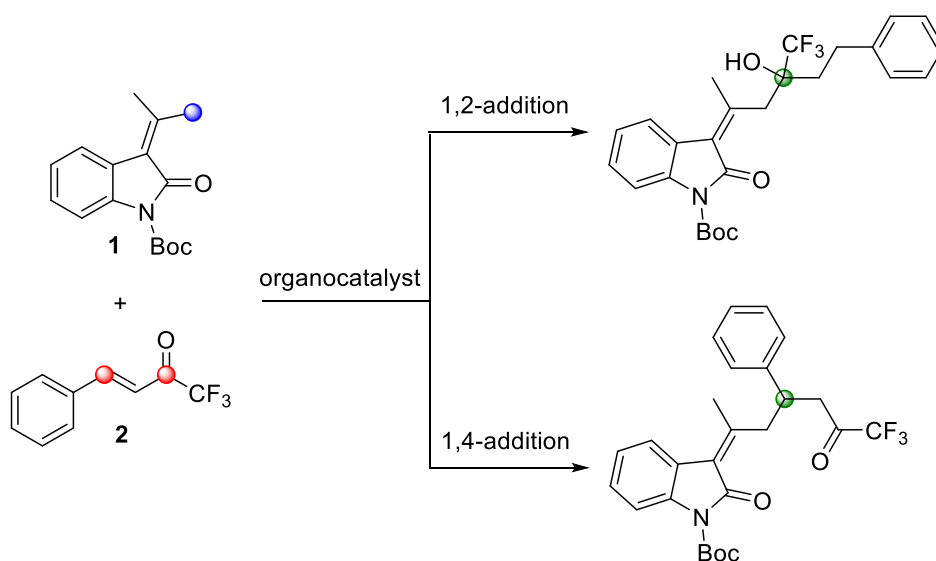


**Scheme 29:** Asymmetric cross-aldol reaction of *o*-hydroxyacetophenones and trifluoromethyl ketones.

All in all, inspired by these studies, our research group became interested in coupling into a single compound 3-alkylidene oxindoles and trifluoromethyl ketones, in order to explore an attractive way to synthesize biologically interesting trifluoromethylated compound.

## 2. AIMS OF THE RESEARCH PROJECT

During my thesis period I focused my studies on the development of an new enantioselective direct vinylogous addition of 3-alkylidene oxindole **1** to  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2**, promoted by bifunctional organocatalysts. Indeed, since several compound containing 3-alkylidene oxindole moiety have exhibited a broad range of biological activity<sup>33,34,35</sup>, the search for new synthetic strategies toward creation of  $\gamma$ -substituted alkylidene oxindoles has triggered our interest. In particular, our goal was to explore the use of different acceptors for vinylogous reactions in which 3-alkylidene oxindoles are employed as nucleophiles. Consequently, our choice has fallen upon trifluoromethyl ketones, which are considered valuable substrates for the synthesis of fluorinated compounds. In fact, nearly one-third of the current drug on market contain fluorine atoms<sup>54</sup>.



**Scheme 30:** Hypothesised products of the enantioselective vinylogous addition of 3-alkylidene oxindole **1** to  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2**. The enolizable site is indicated in blue, while the electrophilic sites are highlighted in red.

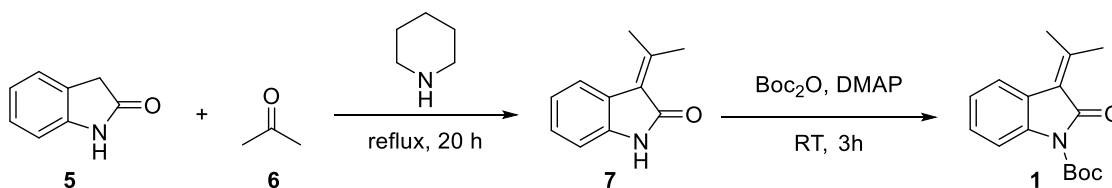
As it is possible to observe in Scheme 30, with  $\alpha,\beta$ -unsaturated carbonyl compounds such as trifluoromethyl ketone **2**, both the carbonyl and the  $\beta$  position are electrophilic site which can react with a nucleophile. The formation of 1,2 or 1,4-addition products depends on multiple variables and, for this reason, we investigated whether the chosen substrates react through direct or

conjugated addition. The reaction would lead to a stereocontrolled formation of optically active compound bearing, in one case, a trifluoromethylated tetrasubstituted carbon stereocenter and in the other, a carbon stereocenter with a  $\alpha$ -trifluoromethyl ketone group. After verifying that the reaction proceeded, we focused on the optimization of various parameters to strengthen it and to make it valuable in terms of yield and enantioselection.

### 3. RESULTS AND DISCUSSION

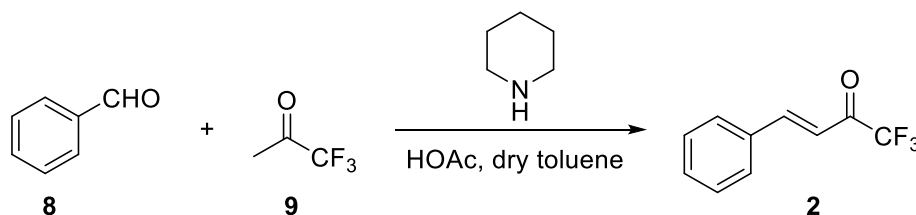
#### 3.1. SYNTHESIS OF THE SUBSTRATES

The 3-alkylidene oxindole **1**, used as nucleophile in the enantioselective vinylogous reaction, was prepared through Knoevenagel condensation, catalysed by piperidine, between oxindole **5** and acetone (**6**) and subsequent Boc-protection of the amino group (Scheme 31)<sup>59</sup>.



**Scheme 31:** Synthesis of the 3-alkylidene oxindole **1**.

On the other hand, the  $\alpha,\beta$ -unsaturated trifluoroketone **2** was synthesized through aldol condensation<sup>60</sup>, promoted by acetic acid and piperidine, between 1,1,1-trifluoroacetone (**9**) and benzaldehyde (**8**). Even if the yield of the reaction is lower than 50 %, the substrates required are cheap and commercially available (Scheme 32).

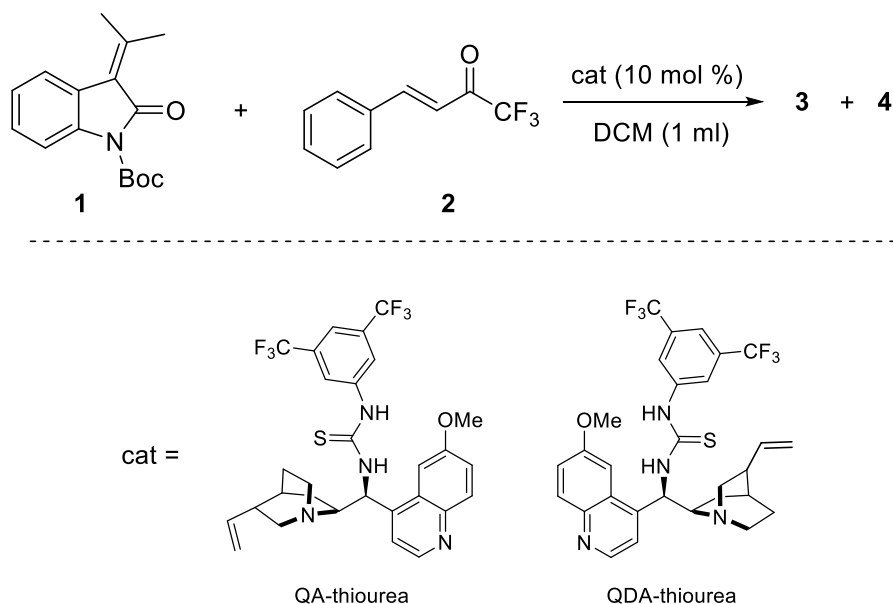


**Scheme 32:** Synthesis of  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2**.



### 3.2. PRELIMINARY REACTION TESTS

In order to test the general reactivity between the substrates chosen, two preliminary reaction tests on a 0.2 mmol scale were conducted, using as catalyst the pseudo-enantiomeric pair quinidine/quinine-thiourea (Table 1).



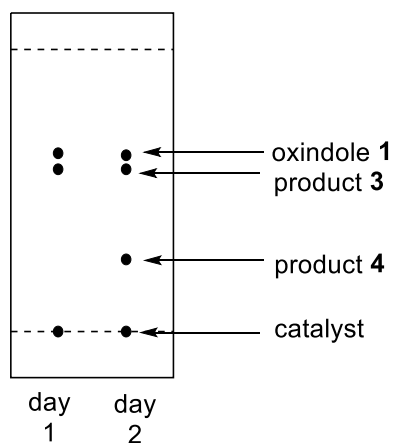
**Table 1:** Preliminary reaction tests

entry	reaction	equivalent 1/2	catalyst	time (d)	yield 3 (%) <sup>a</sup>	yield 4 (%) <sup>a</sup>	3/4 <sup>b</sup>
1	BG045	1:1	QDA- thiourea	2	21	11	9.5 : 1
2	BG046	1:1	QA- thiourea	4	21	11	1.4 : 1

<sup>a</sup>Yields were determined only after assignment of the correct structure of the products through NMR analysis. <sup>b</sup> Determined by <sup>1</sup>H-NMR of the crude mixture after assignment of the correct structure of the products.

The reactions were monitored through TLC and, after 24 h, the analysis showed the presence of a new product (**3**), even if there was still unreacted 3-alkylidene oxindole **1** (Fig. 14). Because of its volatile nature, a small amount of  $\alpha,\beta$ -unsaturated trifluoroketone **2** cannot be properly detected through thin layer chromatography. Only after 48 h, another reaction product (**4**) appeared, even though the starting 3-alkylidene oxindole **1** did not seem to be further consumed.

After 2 days, the reaction catalysed by QDA-thiourea, was filtered on a thin layer of silica (plug) in order to remove the catalyst. In this way, the reaction was interrupted and, after removal of the solvent under reduced pressure, the crude reaction product was obtained.

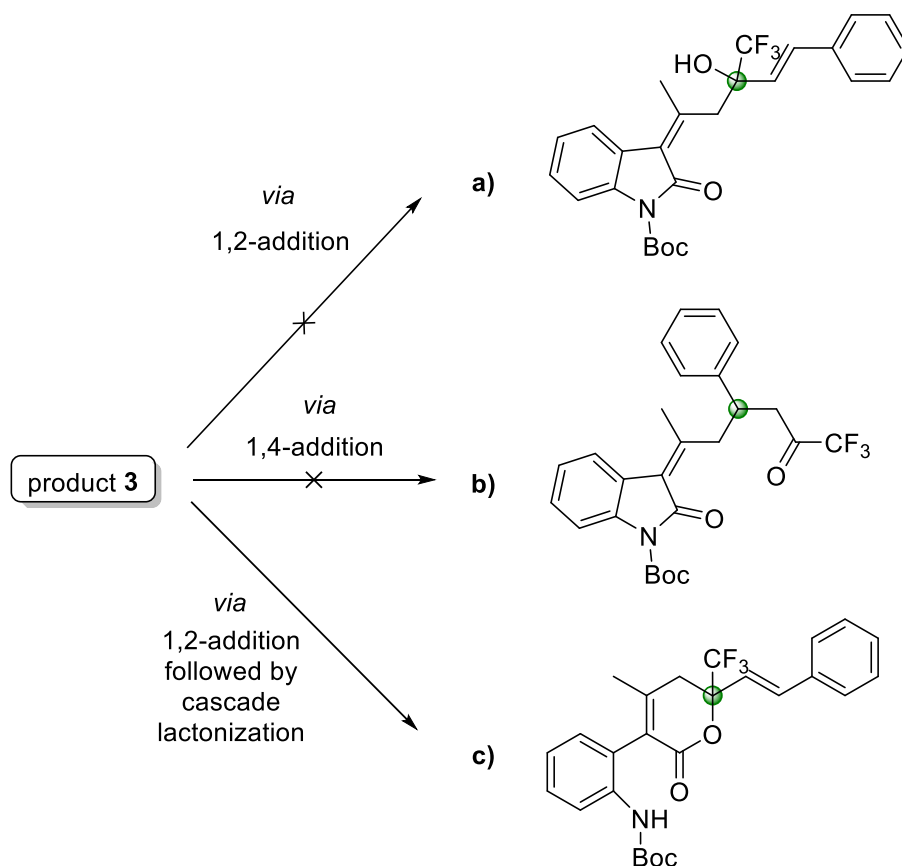


**Fig. 14:** TLC analysis of the preliminary reaction tests.

The reaction promoted by quinine-thiourea was interrupted after 4 days but, through TLC analysis, no further changes were observed in comparison to the reaction plugged two days before.

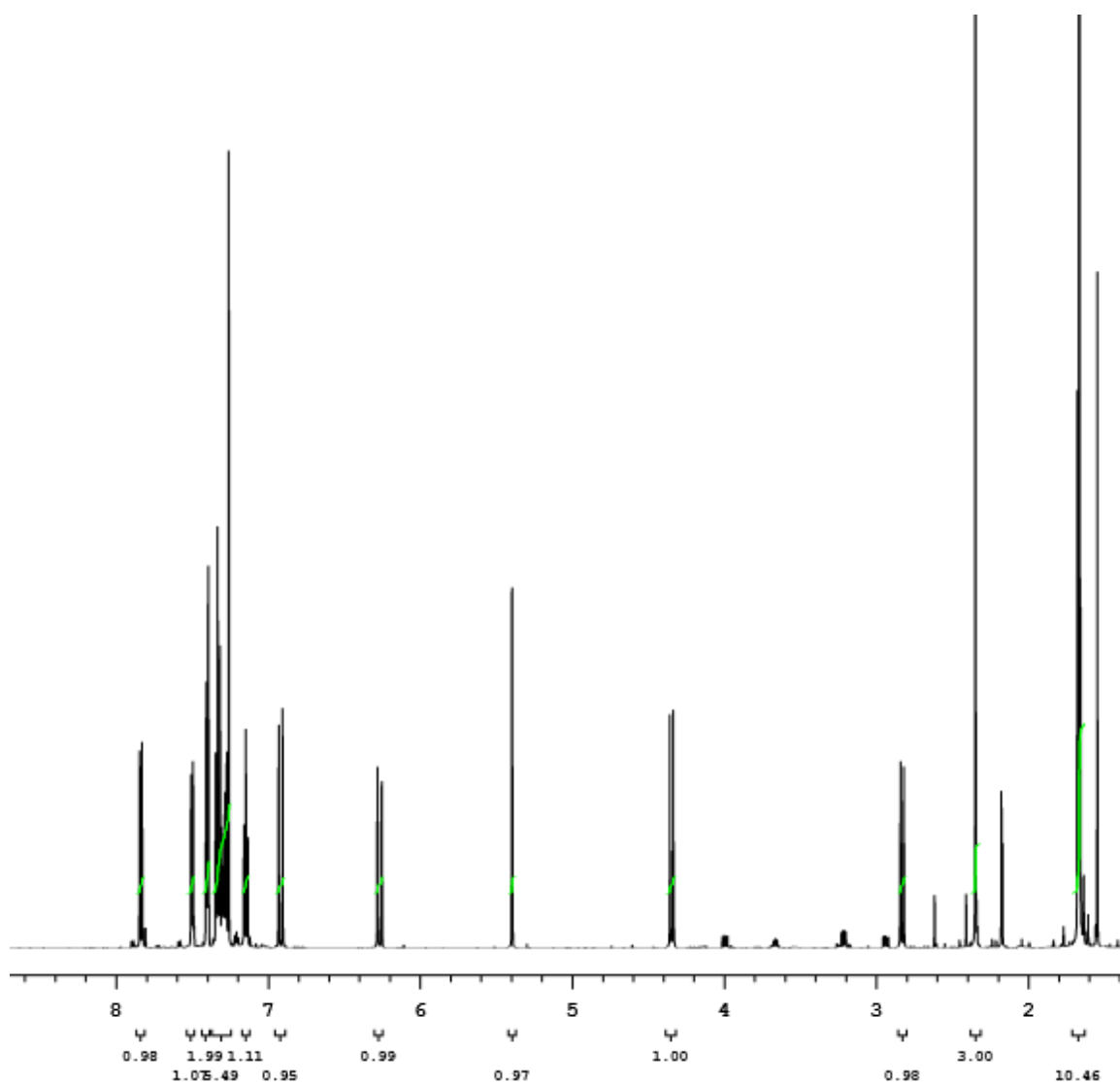
The <sup>1</sup>H-NMR analysis of the crude reaction products revealed the significant presence of the unreacted 3-alkylidene oxindole **1**. All the volatile  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2** is removed when the crude reaction products are dried over vacuo and therefore its signals were not revealed through <sup>1</sup>H-NMR. Besides, the analysis disclosed new signals related to the formation of reaction products. This new products, called **3** and **4**, were then isolated through column chromatography on silica gel and NMR studies were conducted to identify their correct structure.

### 3.3. NMR STUDIES AND IDENTIFICATION OF THE PRODUCTS



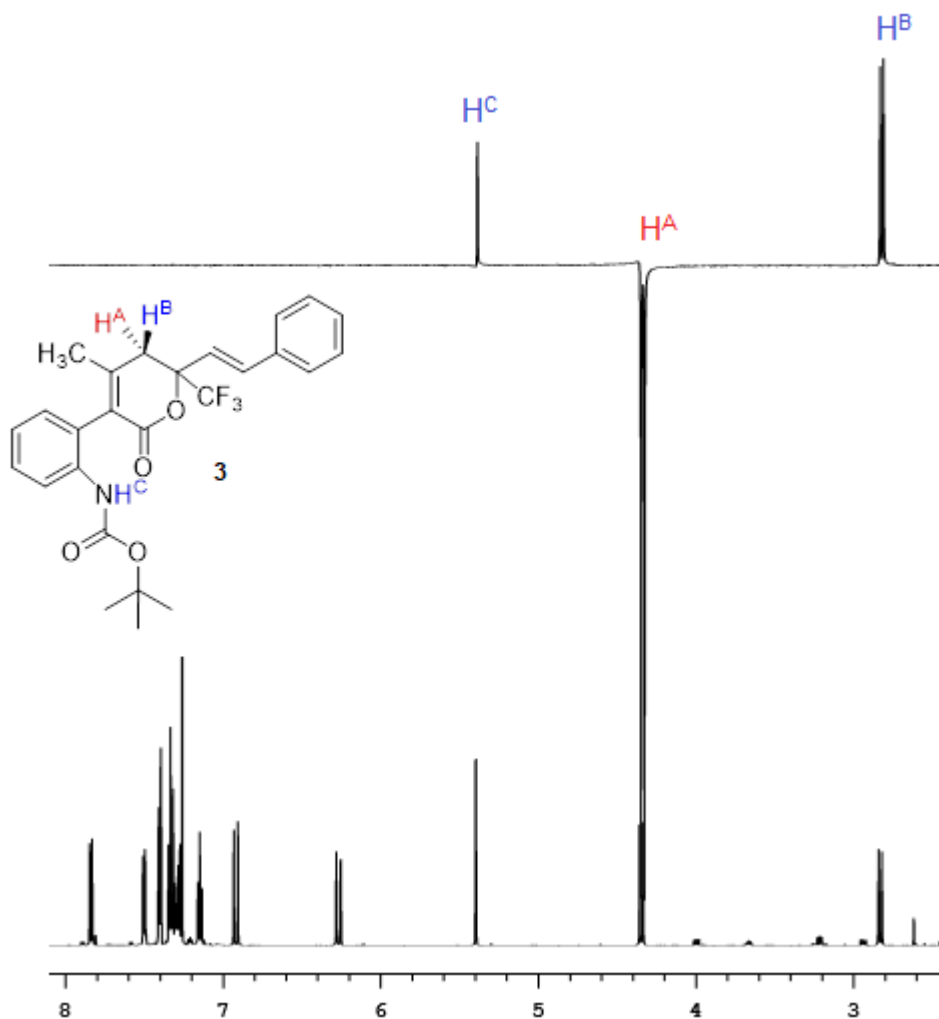
**Fig. 15:** Possible structures of product 3.

Firstly, through <sup>1</sup>H-NMR and <sup>13</sup>C-NMR analysis of compound 3, it was possible to exclude the product of 1,4-addition (Fig. 15b). Indeed, the signals of two CH<sub>2</sub> groups were not observed (Fig. 16). Regarding the 1,2-addition product, the broad singlet typical of the tertiary OH was not detected. On the contrary, the <sup>1</sup>H-NMR spectrum showed a tight singlet at 5.39 ppm which cannot be assigned to aromatic or vinylic protons. Furthermore, the analysis disclosed two doublets with the same coupling constant *J*, which are correspondent to the two diastereotopic protons of the CH<sub>2</sub> group near the asymmetric centre (2.83 and 4.34 ppm). Surprisingly, the distance between these doublets is significantly high (nearly 1.5 ppm) and therefore we reasoned that the CH<sub>2</sub> group might be part of a cyclic structure. Accordingly, we supposed that the product 3 was correspondent to an unsaturated lactone, formed through vinylogous addition followed by cascade intramolecular lactonization (Fig. 15c).



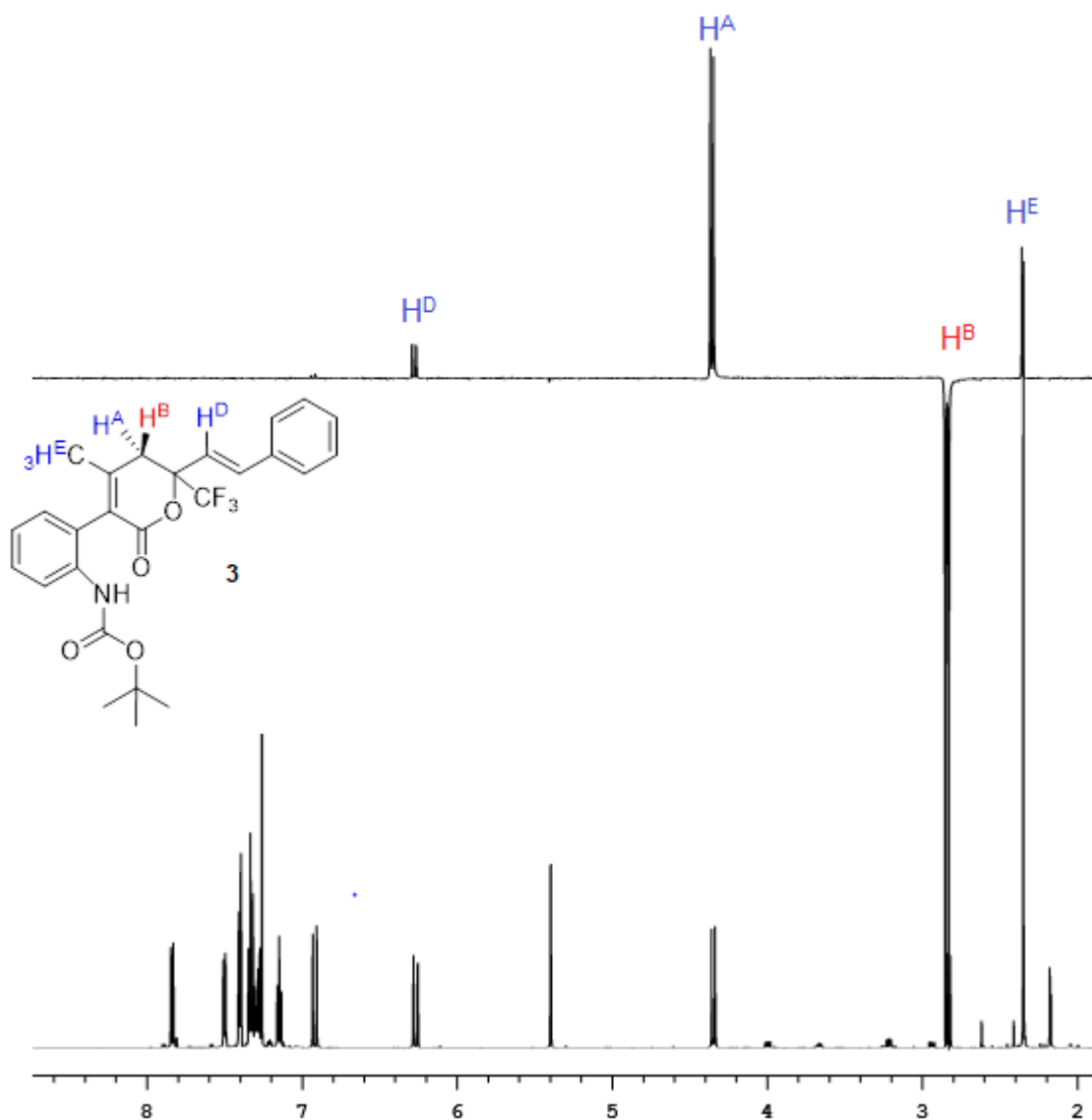
**Fig. 16:** <sup>1</sup>H-NMR spectrum of compound 3.

In order to confirm the assigned structure of the compound 3, NOESY experiments were conducted. NOESY (Nuclear Overhauser Effect Spectroscopy), indeed, is a particular NMR experiment, that is useful for determining which signals arise from protons that are close to each other in space, even if they are not bonded. In this analysis, a signal of the <sup>1</sup>H-NMR spectrum previously acquired is irradiated. The protons which are close to the signal irradiated are subjected to NOE effect and, as a consequence, they can be observed in the spectrum. The most relevant NOESY spectrum performed are illustrated in the Fig. 17 and 18.

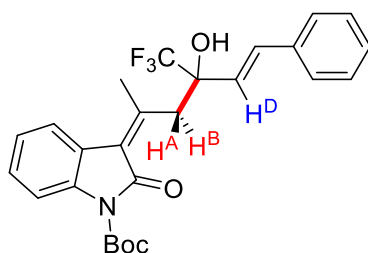


**Fig. 17:** NOE spectra in which the signal at 4.34 ppm is irradiated.

The two diastereotopic protons  $H^A$  and  $H^B$  of the  $CH_2$  group near the asymmetric center, at 2.83 ppm and at 4.34 ppm, were irradiated. In particular, in Fig. 17 and 18 the proton irradiated is highlighted in red, while the protons subjected to NOE effect are indicated in blue. Since it is not possible to distinguish between  $H^A$  and  $H^B$ , we arbitrarily assigned their chemical shift respectively at 4.34 ppm, and 2.83 ppm. The fact that, the vinylic proton  $H^D$  is subjected to NOE effect only when  $H^B$  is irradiated confirmed the presence of a cyclic rigid structure. Indeed, in the case of the product of 1,2 addition (Fig. 19, in the following page) in which the highlighted bond is subjected to rotation,  $H^D$  should be observed in the spectra when both  $H^A$  and  $H^B$  are irradiated.



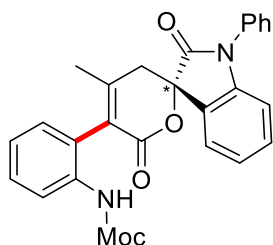
**Fig. 18:** NOE spectra in which the signal at 2.83 ppm is irradiated.



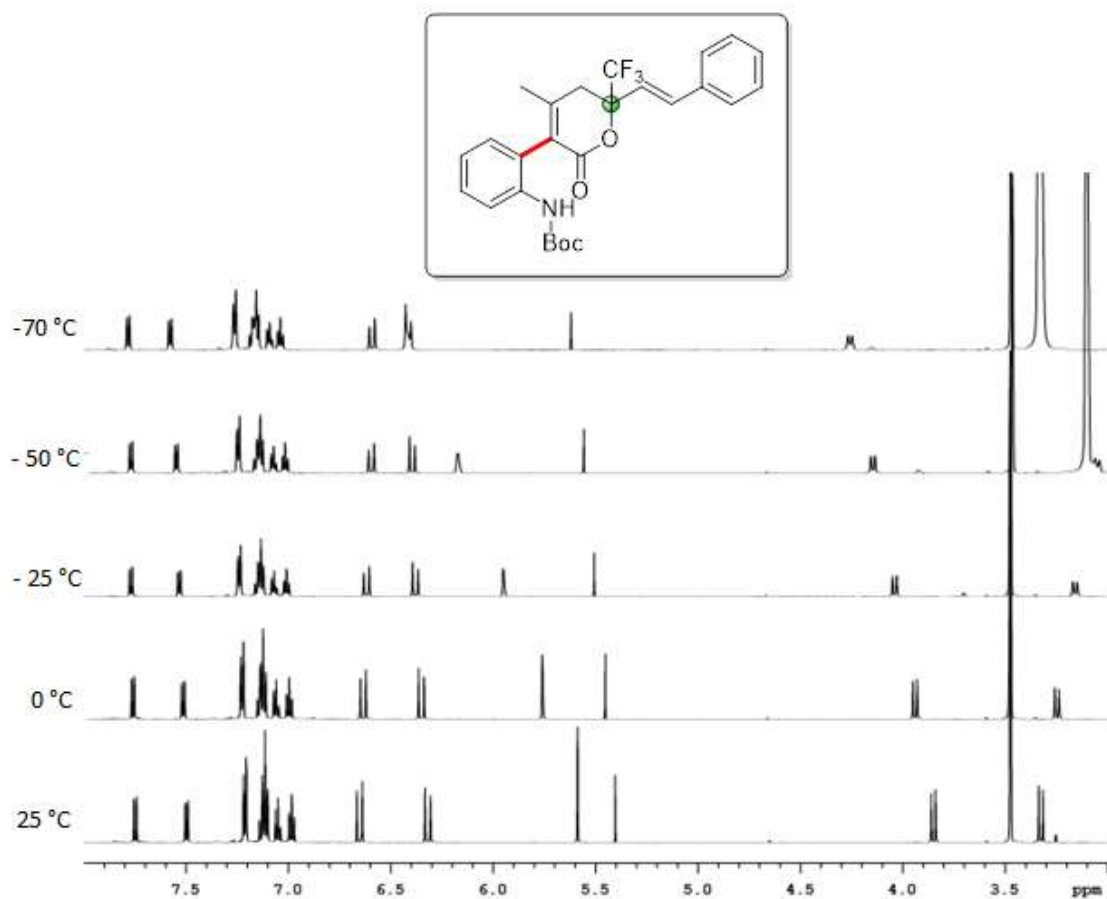
**Fig. 19:** NOE effect in the product of 1,2-addition.

Furthermore, in the  $^1\text{H-NMR}$  of the crude mixture, a set of signals of low intensity that were not correspondent to compound **3** or **4** were observed. We reasoned that they might be attributed to rotational stereoisomers of **3** because, in a previous work of our research group<sup>61</sup>, a structure similar to the unsaturated

trifluoromethyl lactone **3** (Fig. 20) presented conformational stereoisomers due to the hydrogen bond stabilized slow rotation of the aryl-lactone single bond. Hence,  $^1\text{H-NMR}$  experiments of **3** in THF at different temperatures were conducted with the purpose to see if rotational stereoisomers were detected also in our case (Fig. 21).



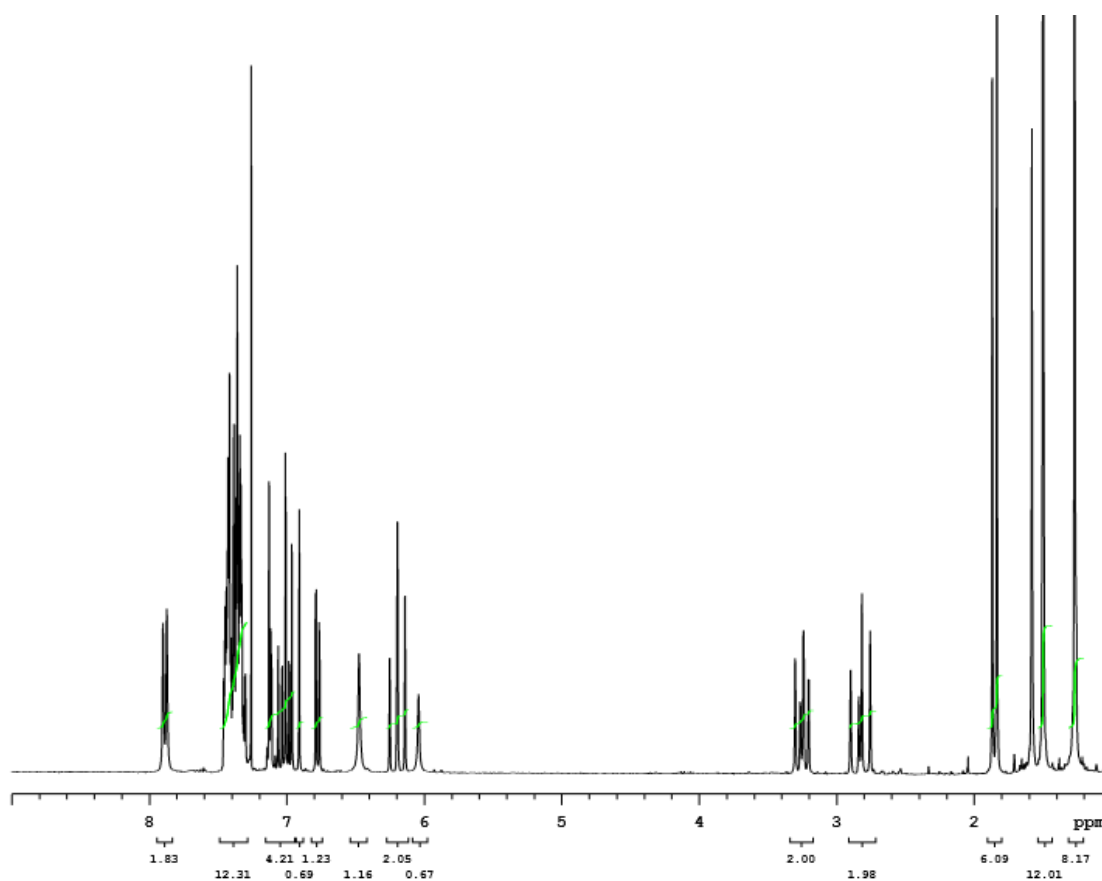
**Fig. 20:** Compound similar to the unsaturated trifluoromethyl lactone **3**.



**Fig. 21:** NMR spectrum of compound **3** in THF at different temperatures.

Unexpectedly, the analysis revealed that, even at  $-70\text{ }^{\circ}\text{C}$ , the signals of the product remained almost unchanged, showing that the rotation around the highlighted red bond in Fig. 21 is not restricted by the steric hindrance. Accordingly, we supposed that these set of signals might be attributed to impurities.

Regarding the structure identification of compound **4**, The spectral analysis  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and DEPT revealed the presence of several NMR duplicate signals: two hydroxyl, two tert-butyl and two methylene groups. Consequently, we concluded that the product **4** was correspondent to a E/Z isomers mixture of the 1,2-addition product (Fig. 23 in the following page).



**Fig. 22:**  $^1\text{H-NMR}$  spectrum of product **4**.



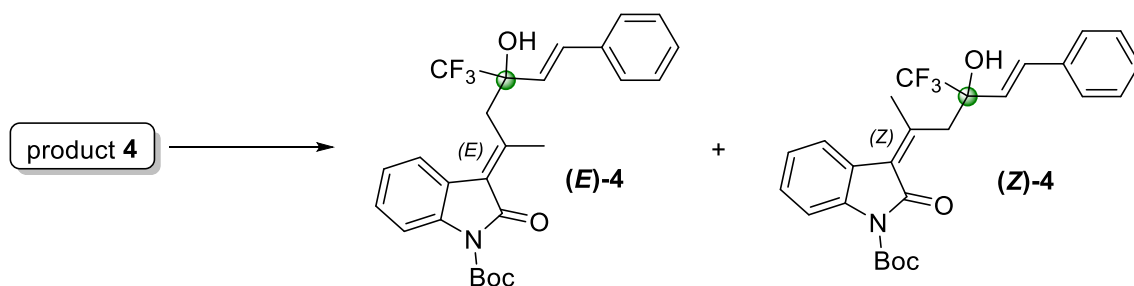


Fig. 23: Structure of product 4

### 3.4. HPLC ANALYSIS OF THE RACEMIC PRODUCT 3 e 4

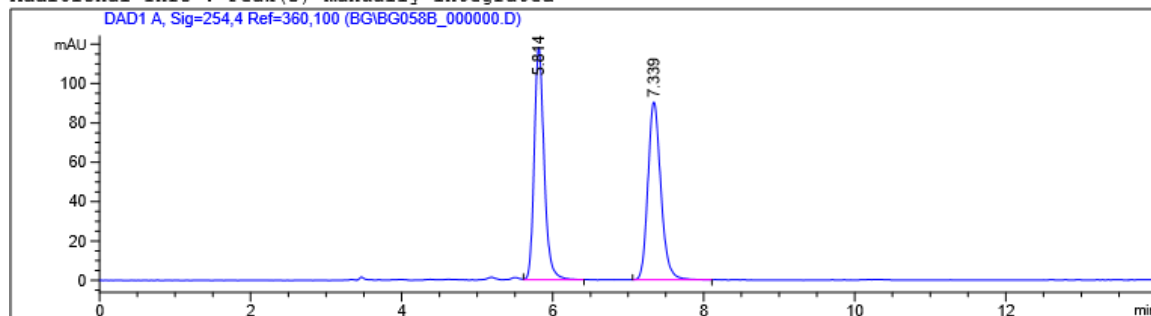
Through HPLC analysis of the racemic **3** on Chiral Pack IC, it was possible to find the best conditions for the separation of enantiomers (eluting: *n*-hexane/isopropanol 95:5, flux: 1ml/min,  $\lambda = 254$  nm) (Fig. 24). Consequently, the enantiomeric excesses of the two preliminary reaction tests were determined: respectively 87 % with QDA-thiourea and 63 % with QA-thiourea (Table 2).

**Table 2:** Enantiomeric excesses of the two preliminary reaction tests.

entry	reaction	catalyst	time (d)	yield 3 (%) <sup>a</sup>	yield 4 (%) <sup>a</sup>	3/4 <sup>b</sup>	ee 3 (%) <sup>c</sup>
1	BG045	QDA-thiourea	2	21	11	9.5 : 1	87
2	BG046	QA-thiourea	4	21	11	1.4 : 1	63

<sup>a</sup>Yields were determined by weighing the purified compounds. <sup>b</sup> Determined by <sup>1</sup>H-NMR of the crude mixture after assignment of the correct structure of the products. <sup>c</sup>Enantiomeric excess were determined through chiral HPLC.

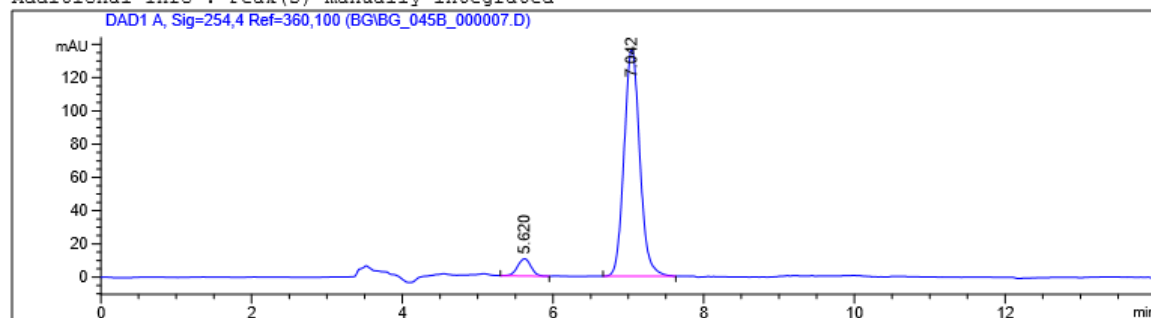
Additional Info : Peak(s) manually integrated



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.814	VB	0.1402	1075.35571	118.18784	49.9549
2	7.339	BB	0.1851	1077.29578	90.32452	50.0451

Fig. 24: HPLC analysis of the racemate **3**.

Additional Info : Peak(s) manually integrated



Additional Info : Peak(s) manually integrated

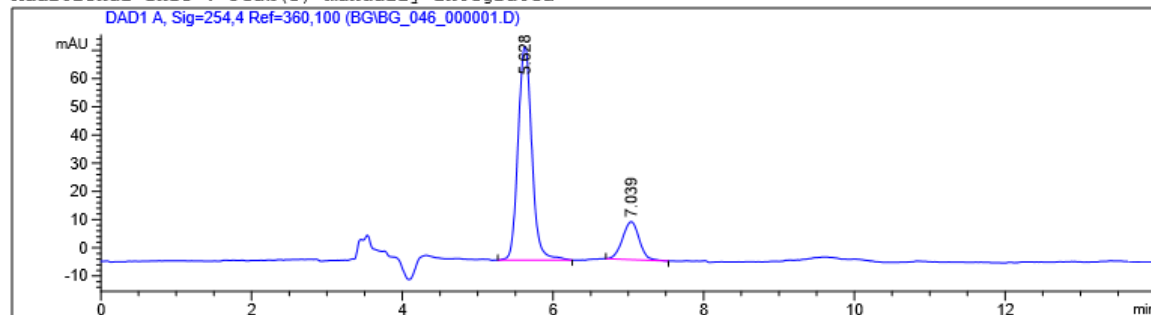
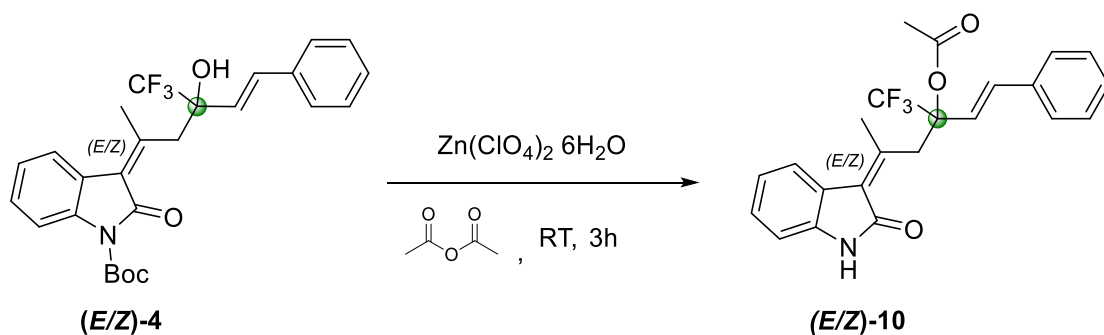


Fig. 25: HPLC analysis of reaction BG045 and BG046 (Table 2).

Unfortunately, the best separation conditions for racemic **4** were not founded. As a result, we tried to acetylate the hydroxyl group in order to afford a compound separable through chiral HPLC. For this purpose, racemic **4** was solubilized in acetic anhydride and 0.7 equivalents of  $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  were then added. After stirring the reaction mixture at room temperature for 3 hours, the solvent was evaporated under reduced pressure. Afterwards, the residue was purified by column chromatography on silica gel to afford compound **10** (Scheme 33). The

NMR spectrum of the product **10** was consistent with the structure depicted in Scheme 33. Indeed, although the acetylation was successful, the acidic conditions caused the removal of the Boc-group. Unluckily, chiral HPLC analysis of the obtained product **10** gave negative results and therefore it was not possible to assess the enantiomer excess of compound **4**.

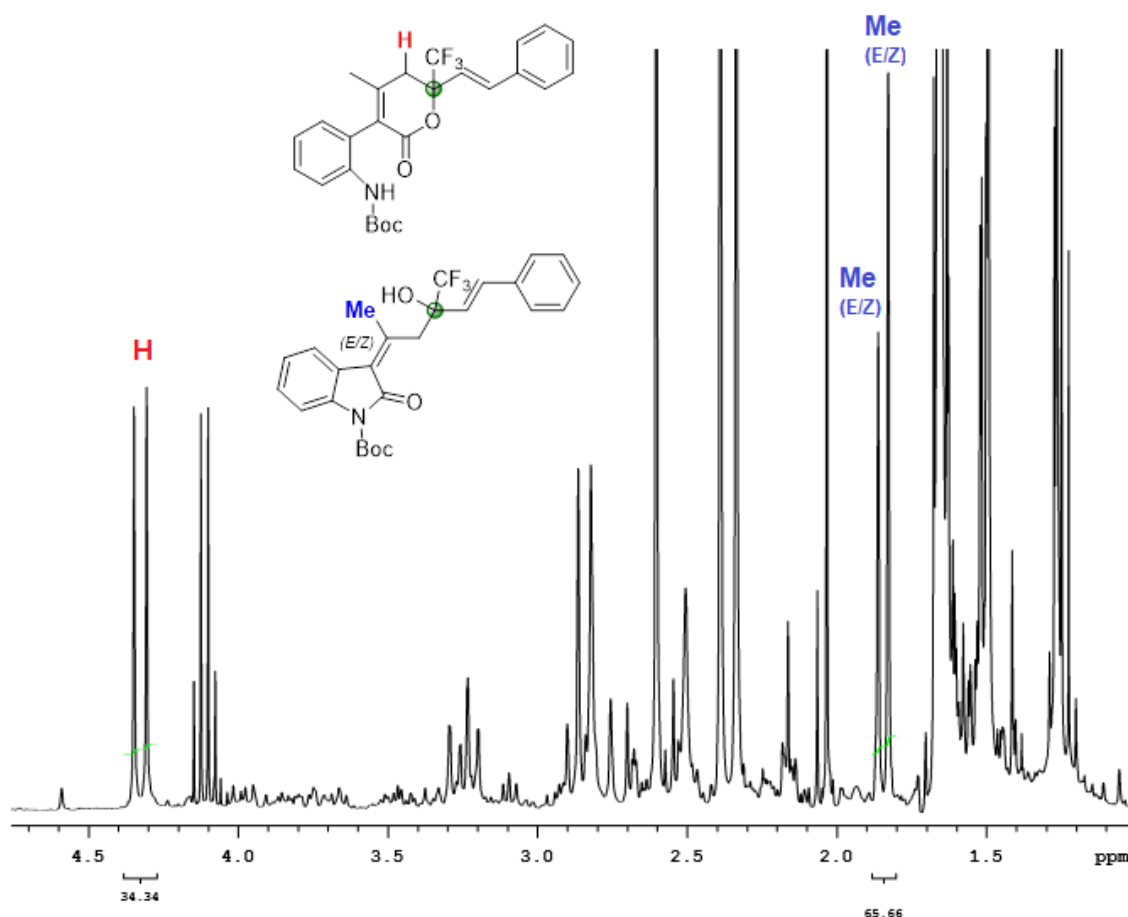


**Scheme 33:** Acetylation of compound **4**.

### 3.5. SCREENING OF THE CATALYST

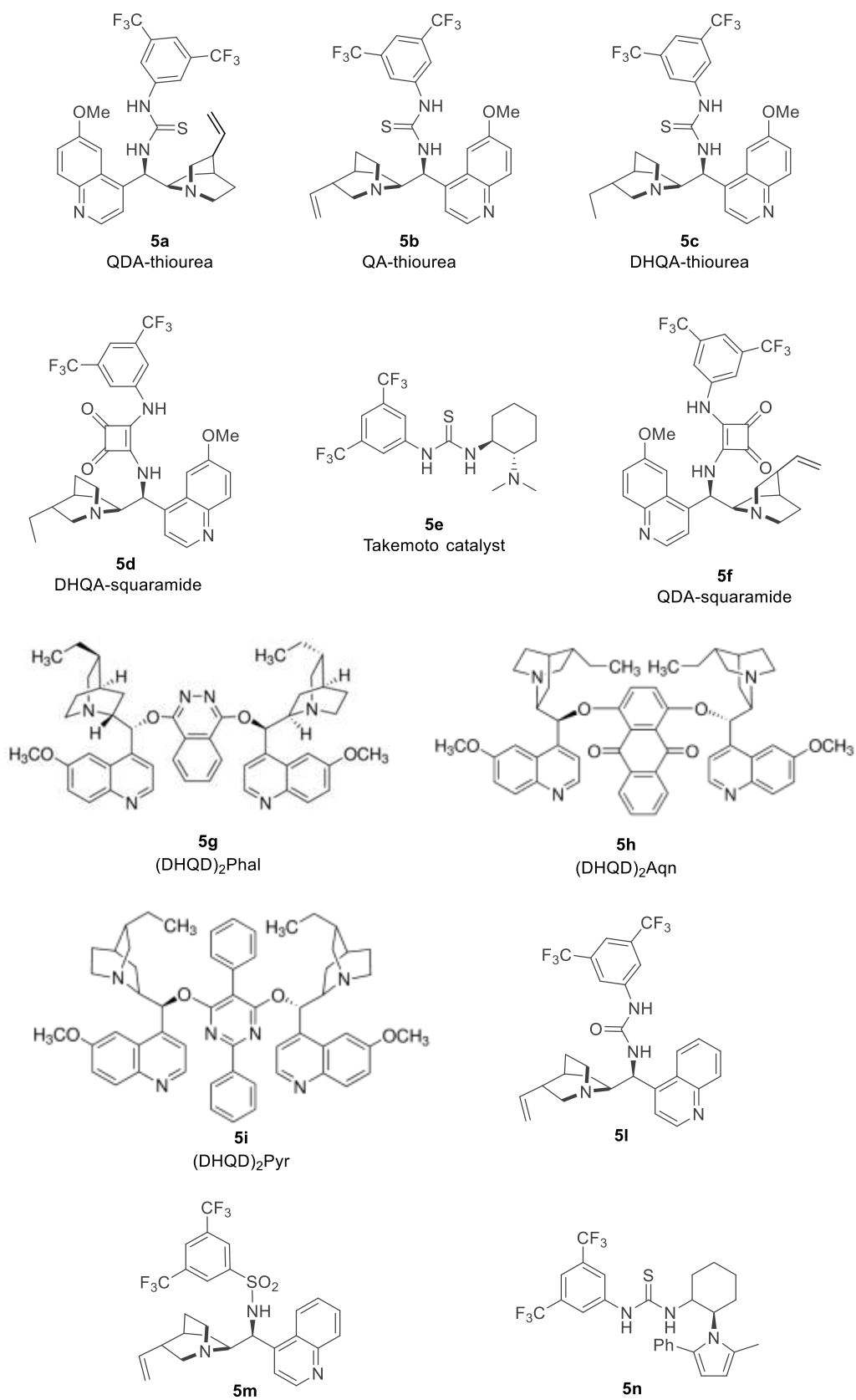
In asymmetric synthesis, the search for the best catalyst is of utmost importance, indeed the catalyst is the major responsible for the enantiomeric enrichment. For this reason, the first reaction parameter screened was the organocatalyst and the screening was performed as follows: the reaction mixture composed of a solution in DCM of 3-alkylidene oxindole **1**,  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2** and the catalyst was stirred at room temperature for the necessary time. Subsequently, the reaction mixture was plugged over silica gel in order to eliminate the catalyst and the products were isolated through column chromatography. After isolation, enantiomer excesses of the unsaturated lactone **3** were determined by chiral HPLC analysis on Chiral Pack IC (hexane-isopropanol 95:5, flux: 1 ml/min,  $\lambda = 254$  nm). The yields of the products were determined by weighing the purified compounds. The ratio between product **3** and **4** was evaluated through  $^1\text{H-NMR}$  of the crude mixture (Fig. 26), integrating the following signals:

- the doublet at 4.34 ppm, that correspond to one hydrogen of compound **3**.
- the two singlets at 1.83 and 1.87 ppm, which are correspondent to six hydrogens of product **4**.

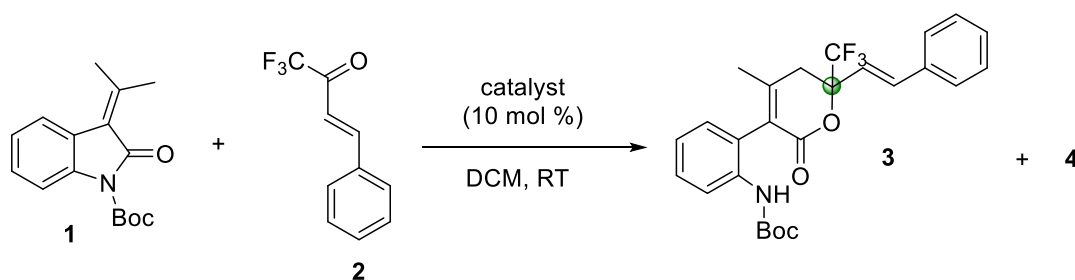


**Fig. 26:** Evaluation of **3/4** through <sup>1</sup>H-NMR of the crude mixture.

The promising enantiomer excesses obtained in the preliminary reaction tests, using as catalyst QDA/QA-thiourea (**5a**, **5b**), encouraged us to search a catalyst able to give an higher enantiomer excess and especially an higher yield. In Fig. 27 all the structures of the catalysts tested are shown, while in Table 3 all the enantiomer excesses and the yield of all the reactions conducted are reported.



**Fig. 27:** Structures of the catalysts tested.



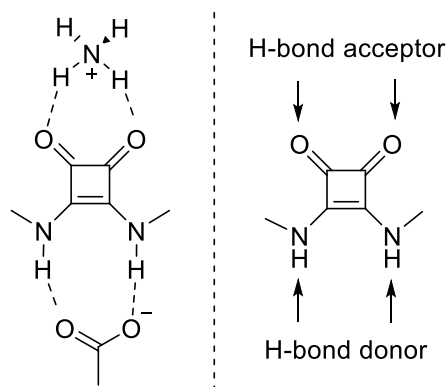
**Table 3:** Screening of the catalyst.

entry	reaction	catalyst	time (d)	yield 3 (%) <sup>a</sup>	yield 4 (%) <sup>a</sup>	ratio 3/4 <sup>b</sup>	ee 3 (%) <sup>c</sup>
1	BG045	5a	2	21	11	9.5 : 1	87
2	BG046	5b	4	21	11	1.4 : 1	63
3	BG066	5c	1	32	nd	3 : 1	91
4	BG059	5d	4	12	nd	1 : 1.8	65
5	BG060	5e	4	38	nd	2.8 : 1	80
6	BG061	5f	4	42	nd	3.5 : 1	75
7	BG062	5g	4	-	-	-	-
8	BG063	5h	4	-	-	-	-
9	BG064	5i	4	-	-	-	-
10	BG084	5l	1	31	nd	5.2 : 1	91
11	BG085	5m	4	-	-	-	-
12	BG086	5n	4	-	-	-	-

<sup>a</sup>Yields were determined by weighing the purified compounds. <sup>b</sup>Determined by <sup>1</sup>H- NMR of the crude mixture. <sup>c</sup>Enantiomeric excess were determined through chiral HPLC. nd = not determined and not available.

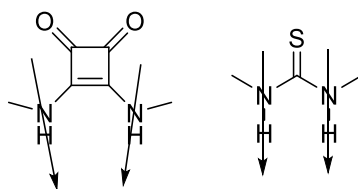
As it is possible to observe from Fig. 27, many of the catalysts tested are chiral bifunctional thioureas/ureas which are able to activate the reacting molecules simultaneously (**5a**, **5b**, **5c**, **5e**, **5l**, **5n**). In particular, the basic moiety of the catalyst generate the nucleophile, while the electrophile is activated via hydrogen-bonding interactions. Moreover, also bifunctional catalysts possessing squaramide moiety (**5d**, **5f**) were explored. Indeed, squaramides act as efficient bifunctional catalysts for a number of important enantioselective organic transformations and, in comparison to their analogue thioureas, they have obtained greater results, especially in terms of turn-over number. However,

squaramides differs significantly from their correspondent thioureas in five aspects: 1) duality in ion- and H-bonding; 2) rigidity; 3) H-bond spacing; 4) H-bond angle, and 5) pKa<sup>62</sup>. Firstly, squaramides are also “bifunctional” in their H-bonding properties: in fact they possess two hydrogen-bond donors (N-H) and two carbonyl acceptors (C=O) (Fig. 28).



**Fig. 28:** Duality in hydrogen-bonding of squaramides.

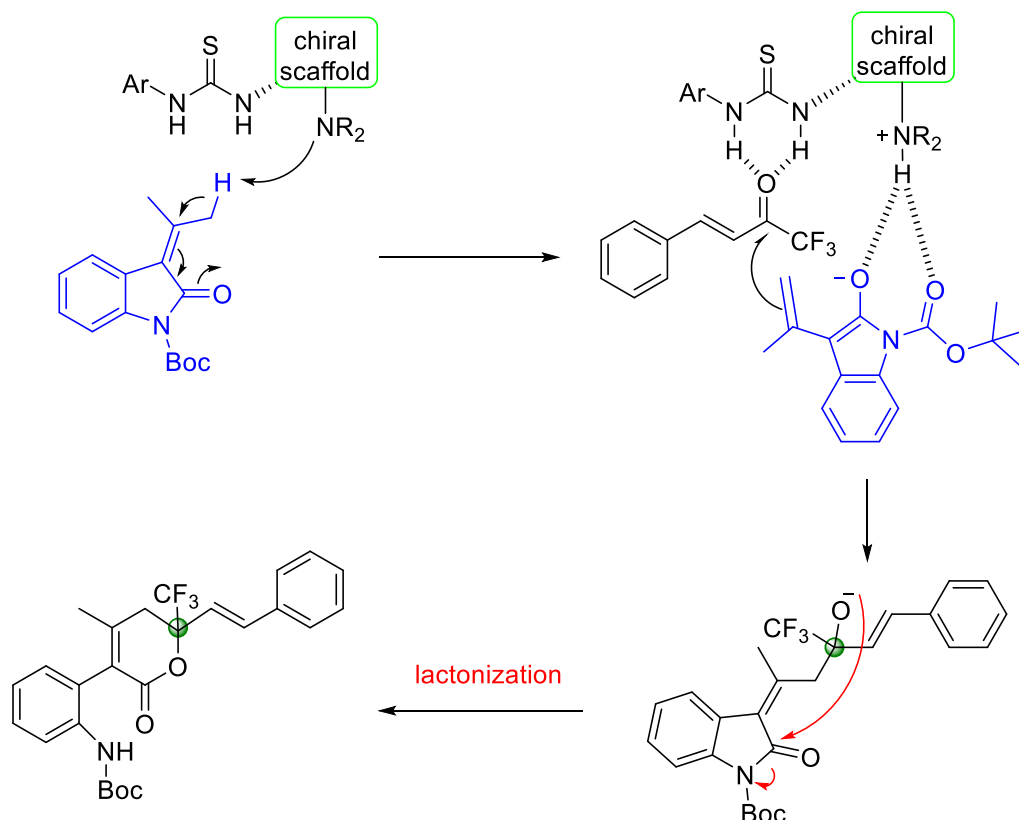
The ability to be H-bond acceptors is due to the fact that, upon complexation, the aromatic character of the four-membered ring increases. Moreover, the increased rigidity of the squaramide moiety is explained by the further delocalization of the nitrogen ion pair through the partially aromatic cyclobutenedione system, with a consequent restricted rotation of the C-N bond. Another significant difference between thioureas and squaramides is the relative distance and spacing between the two N-H groups (2.13 Å for N,N'-dimethylthiourea and 2.72 Å for N,N'-dimethylsquaramide). Furthermore, the particular square structure of the cyclobutenedione ring induces a convergent orientation of the N-H groups, (approximately 6°) (Fig. 29).



**Fig. 29:** Disposition of the hydrogen bonds in squaramides and thioureas.

In addition, The N-H protons of squaramide are more acidic than the ones of thioureas, in fact, the pKa values of the acidic N-H protons in the squaramide are

lower than the pKa values of H<sub>2</sub>CO<sub>3</sub> and squaric acid<sup>62</sup>. However, in our case, the use of bifunctional squaramide (**5d** and **5f**) have a negative impact on the enantioselectivity. With squaramide **5d** (entry 4) the desired product was afforded in low yield (12 %). On the other hand, despite the moderate enantiomer excess (75 %), the reaction with squaramide **5f** (entry 6) gave the best result in terms of yield. In order to investigate the relevant role of hydrogen-bonding interactions in the activation of the substrates, catalyst without hydrogen-bond donor groups were tested (catalyst **5g**, **5h** and **5i**). It appeared that these catalysts did not provide the reaction products (entries 7, 8, and 9). Accordingly, these results suggested that activation of both the 3-alkylidene oxindole and  $\alpha,\beta$ -unsaturated trifluoromethyl ketone was necessary, as it possible to observe in the scheme below (Scheme 34).



**Scheme 34:** Proposed activation mechanism for the vinylogous addition followed by cascade lactonization of 3-alkylidene oxindole **1** to  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2**.

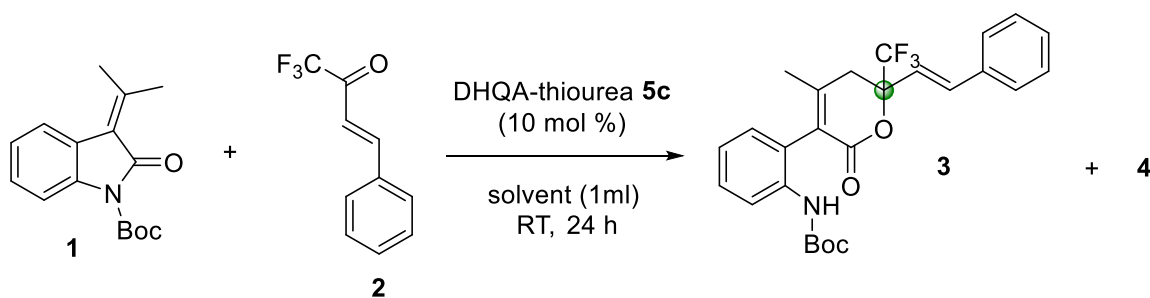


In addition, also catalyst **5m**, provided with only one hydrogen-bond donor group, was employed, showing no reaction (entry 11). In comparison to the other thiourea catalysts explored (**5e**), no products were obtained using an aromatic catalyst **5n** (entry 12). Probably, the aromatic nitrogen of this catalyst is not sufficiently basic to form the dienolate of the 3-alkylidene oxindole **1**.

Altogether, the higher enantiomer excess (91 %) was observed with DHQA-thiourea (catalyst **5c**, entry 3) and therefore **5c** was employed as catalyst in the solvent screening, with the purpose to find the best reactions conditions. In particular, the yield of the reaction is low (32 %) and, for this reason, we then focused our attention in the improvement of this parameter. Besides, from the table is evident that higher reaction time correspond to lower ratio 3/4 and, as a consequence, for the other screening we interrupted all the reactions after 24 hours.

### 3.6. SCREENING OF THE SOLVENT

The choice of solvent can have a significant effect on the performance of a reaction. In fact, in many cases the polarity and ability of the solvent to stabilise the reaction intermediate is of paramount importance. Consequently, this screening is aimed to find the most effective solvent for our reaction in terms of yield and enantiomer excess. In Table 4 the obtained results are reported; all the reactions were carried out in the same standard conditions depicted (0.2 mmol scale, equivalent ratio between reagents 1:1, reaction time of 24 h).



**Table 4:** Screening of the solvent.

entry	reaction	solvent	dielectric constant ( $\epsilon$ )	yield <b>3</b> (%) <sup>a</sup>	yield <b>4</b> (%) <sup>a</sup>	ratio <b>3/4</b> <sup>b</sup>	ee <b>3</b> (%) <sup>c</sup>
1	BG066	DCM	8.93	32	nd	3 : 1	91
2	BG096	DCM <sup>d</sup>	8.93	11	40	1 : 1.4	72
3	BG089	CHCl <sub>3</sub>	4.81	18	15	3.3 : 1	85
4	BG090	trifluorotoluene	9.18	10	56	1 : 3	61
5	BG091	1,2-dichloroethane	10.5	6	38	1 : 2.2	66
6	BG092	dry THF	7.58	38	traces	13.4 : 1	92
7	BG093	toluene	2.38	15	41	1 : 2	69
8	BG094	CH <sub>3</sub> CN	37.5	3	59	1 : 9	56
9	BG095	MTBE	2.6	38	28	3 : 1	89
10	BG100	DIPE	3.8	16	26	1.6 : 1	75

<sup>a</sup>Yields were determined by weighing the purified compounds. <sup>b</sup>Determined by <sup>1</sup>H-NMR of the crude mixture. <sup>c</sup>Enantiomeric excess were determined through chiral HPLC. <sup>d</sup>The reaction is carried out in the presence of 30 mg of 4 Å activated molecular sieves.

As it is possible to note from Table 4, the solvent has a great influence on the selectivity of the reaction. For instance, the use of trifluorotoluene, 1,2-dichloroethane, toluene, CH<sub>3</sub>CN and DIPE as solvents (entry 4, 5, 7, 8, 10) provided principally the product of 1,2-direct addition **4**. Especially, in CH<sub>3</sub>CN compound **4** is almost the only product formed, with a yield of 59 % (entry 8). On the other side, in dry THF the major product obtained is the unsaturated lactone **3** (entry 6). These data suggested that there is no correlation between the polarity of the solvent and the selectivity of the reaction.

Considering the results obtained in dry THF (entry 6), in order to verify if the absence of water could promote the formation of compound **3**, it was decided to carry out the reaction in DCM in the presence of 30 mg of 4 Å activated molecular sieves (entry 2). Unfortunately, compound **4** was the major product of this reaction and the unsaturated lactone **3** was afforded in low yield and enantiomer excess. Moreover, from table 4, it possible to note that when the yield of product **3** decrease (lower ratio **3/4**), also its enantiomer excess significantly decline.

Since it was not possible to assess the ee of the product **4**, our interest focused on the obtainment of the unsaturated lactone **3** and, for this purpose, dry THF was considered the most effective solvent (entry 6). However, even if the enantiomer excess is high (92 %) the yield remains lower than 40 %.

### 3.7. SCREENING OF REACTION CONDITIONS

Further experiments were performed to study the dependence of our reaction toward catalytic loading, volume of solvent, concentration of reagents, reaction time, stoichiometry of reagents employed and temperature. In this cases, we left unchanged the solvent (dry THF) and the catalyst used (DHQA-thiourea), varying all the other possible parameters.

Firstly, different test with various concentration of catalyst and volumes of solvent were conducted (Table 5).

**Table 5:** Screening of reagents concentration and catalytic loading.

entry <sup>a</sup>	reaction	catalytic loading (%)	volume of solvent (ml)	yield 3 (%) <sup>b</sup>	yield 4 (%) <sup>b</sup>	ratio 3/4 <sup>c</sup>	ee 3 (%) <sup>d</sup>
1	BG092	10	1	38	traces	13.4 : 1	92
2	BG097	5	1	26	traces	> 19 :1	88
3	BG098	5	0,5	42	traces	> 19 :1	93
4	BG099	5	2	30	traces	> 19 :1	89

<sup>a</sup>All the reactions were interrupted after 24h. <sup>b</sup>Yields were determined by weighing the purified compounds. <sup>c</sup>Determined by <sup>1</sup>H-NMR of the crude mixture. <sup>d</sup>Enantiomeric excess were determined through chiral HPLC.

We found that the best results is provided by using a catalytic loading of 5 mol % in 0.5 ml of dry THF (entry 3). For this reason, we investigated the dependence of the reaction toward the reaction time, maintaining the same conditions employed in entry 3 (Table 6).

**Table 6:** Screening of the reaction time.

entry	reaction	time (days)	yield 3 (%) <sup>a</sup>	yield 4 (%) <sup>a</sup>	ratio 3/4 <sup>b</sup>	ee 3 (%) <sup>c</sup>
1	BG098	1	42	Traces	> 19 :1	93
2	BG101	2	30	27	7.7 :1	91
3	BG102	3	35	10	6.6 :1	91
4	BG103	6	36	8	6.5 : 1	91

<sup>a</sup>Yields were determined by weighing the purified compounds. <sup>b</sup>Determined by <sup>1</sup>H-NMR of the crude mixture. <sup>c</sup>Enantiomeric excess were determined through chiral HPLC.

From the data reported in Table 6 is clearly evident that after 24 hour the 1,2-addition product **4** was formed and consequently there was a decreased in the yield of **3** (lower ratio 3/4) (entry 2,3 and 4). Hence, for the others experiments, we left unchanged the reaction time (24 hours, entry 1).

Afterwards, the dependence of our reaction toward stoichiometry of reagents was examined (Table 7).

**Table 7:** Screening of the equivalent ratio between the reagents **1** and **2**.

entry <sup>a</sup>	reaction	equivalents 1/2	yield 3 (%) <sup>b</sup>	yield 4 (%) <sup>b</sup>	ratio 3/4 <sup>c</sup>	ee 3 (%) <sup>d</sup>
1	BG098	1:1	42	traces	> 19 :1	93
2	BG105	1:2	42	39	9.3 : 1	92
3	BG106	2:1	33	16	12.4 : 1	93

<sup>a</sup>All the reactions were interrupted after 24h. <sup>b</sup>Yields were determined by weighing the purified compounds. <sup>c</sup>Determined by <sup>1</sup>H-NMR of the crude mixture. <sup>d</sup>Enantiomeric excess were determined through chiral HPLC.

When the reaction is performed with an excess of 3-alkylidene oxindole **1** the desired product **3** is obtained in a lower yield (33 %) (entry 3). No indicative differences are reported in terms of yield and ee (%) of the product **3** between the reaction carried out with an excess of the  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2** (entry 2) and the reaction carried out with an equivalent ratio between the reagents 1:1 (entry 1). However, in the reaction conditions used in entry 1 the

ratio **3/4** is higher. Consequently, we concluded that the best equivalent ratio between the reagent is 1:1.

Finally, the influence of temperature on the reaction parameters was investigated (Table 8).

**Table 8:** Screening of temperatures.

entry <sup>a</sup>	reaction	temperature (°C)	yield 3 (%) <sup>b</sup>	yield 4 (%) <sup>b</sup>	ratio 3/4 <sup>c</sup>	ee 3 (%) <sup>d</sup>
1	BG098	25	42	traces	> 19 : 1	93
2	BG108	40	23	18	5.5 : 1	91
3	BG109	0	24	traces	> 19 : 1	95

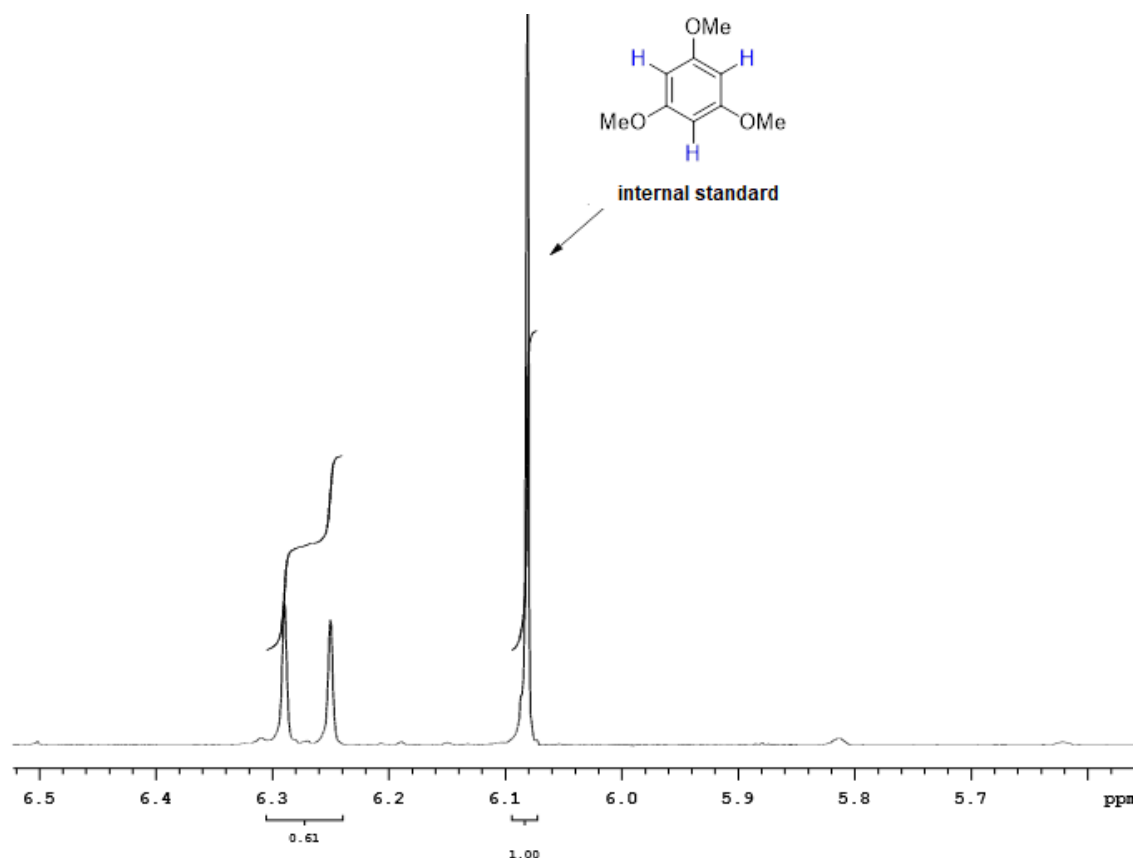
<sup>a</sup>All the reactions were interrupted after 24h. <sup>b</sup>Yields were determined by weighing the purified compounds. <sup>c</sup>Determined by <sup>1</sup>H-NMR of the crude mixture. <sup>d</sup>Enantiomeric excess were determined through chiral HPLC.

The highest enantiomer excess (95 %) was afforded when the reaction was performed at 0 °C. Nevertheless, the low temperatures generally slow down the reaction rate and therefore, in this case, the yield is low (24 %). On the other hand, the reaction carried out at 40 °C formed compound **4** and the desired product **3** in a low yield (23 %). Hence, we concluded that the best reaction conditions are the ones employed in entry **1**. However, the main limit of the reaction consists in the moderate yield (42 %).

**Table 9:** Optimized reaction conditions.

<b>Reaction</b>	BG098
<b>Equivalent ratio between 1 and 2</b>	1:1
<b>Catalyst</b>	DHQA-thiourea
<b>Solvent</b>	Dry THF (0,5 ml)
<b>Time</b>	1 day
<b>Temperature</b>	25 °C
<b>Yield 3 (%)</b>	42
<b>Ratio 3/4</b>	> 19: 1
<b>ee 3 (%)</b>	93
<b>Molarity</b>	0,4 M

Moreover, in view of the discrepancy between the yields determined by weighing and the ratio of **3/4** determined through  $^1\text{H-NMR}$  of the crude mixture, we decided to calculate the yield of compound **3** by the use of an internal standard, such as 1,3,5-trimethoxybenzene (Fig. 30).



**Fig. 30:** Evaluation of yield **3** through  $^1\text{H-NMR}$  of the crude mixture.

We disclosed that the yield of compound **3** (61 %) was significantly higher than the one determined after chromatography (42 %) and, as a consequence, we concluded that the unsaturated lactone might be subjected to degradation during the purification by column chromatography on silica gel. Probably, the acidity of silica gel favours the conversion of cyclic product **3** in the open one **4**.

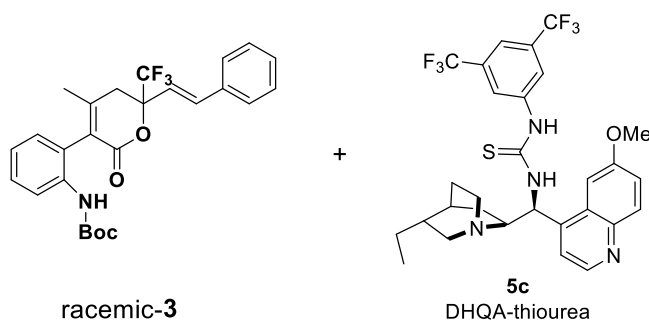
In conclusion, with the optimized reaction conditions in hand (Table 9 in the previous page), we focused our attention on the comprehension of the reaction mechanism.

### 3.8. STUDIES ON THE REACTION MECHANISM

Initially, we wanted to ensure that the  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2** did not degrade in the presence of the catalyst. For this purpose, to a solution of 20 mmol of trifluoromethyl ketone **2** in 0.5 ml of  $\text{CDCl}_3$  were added 2 mmol of catalyst **5e** and 20 mmol of dibromomethane as an internal standard. The development of the reaction was followed through  $^1\text{H-NMR}$  and no degradation of the reagent **2** was observed.

Subsequently, the interaction between the catalyst and the unsaturated lactone **3** was examined. In particular, the enantiomer excess of a mixture of racemic **3** and DHQA-thiourea (equivalent ratio 1:1) in DCM was monitored through chiral HPLC (Table 10).

**Table 10:** Effect on the ee of **3** with the presence of **5c**.

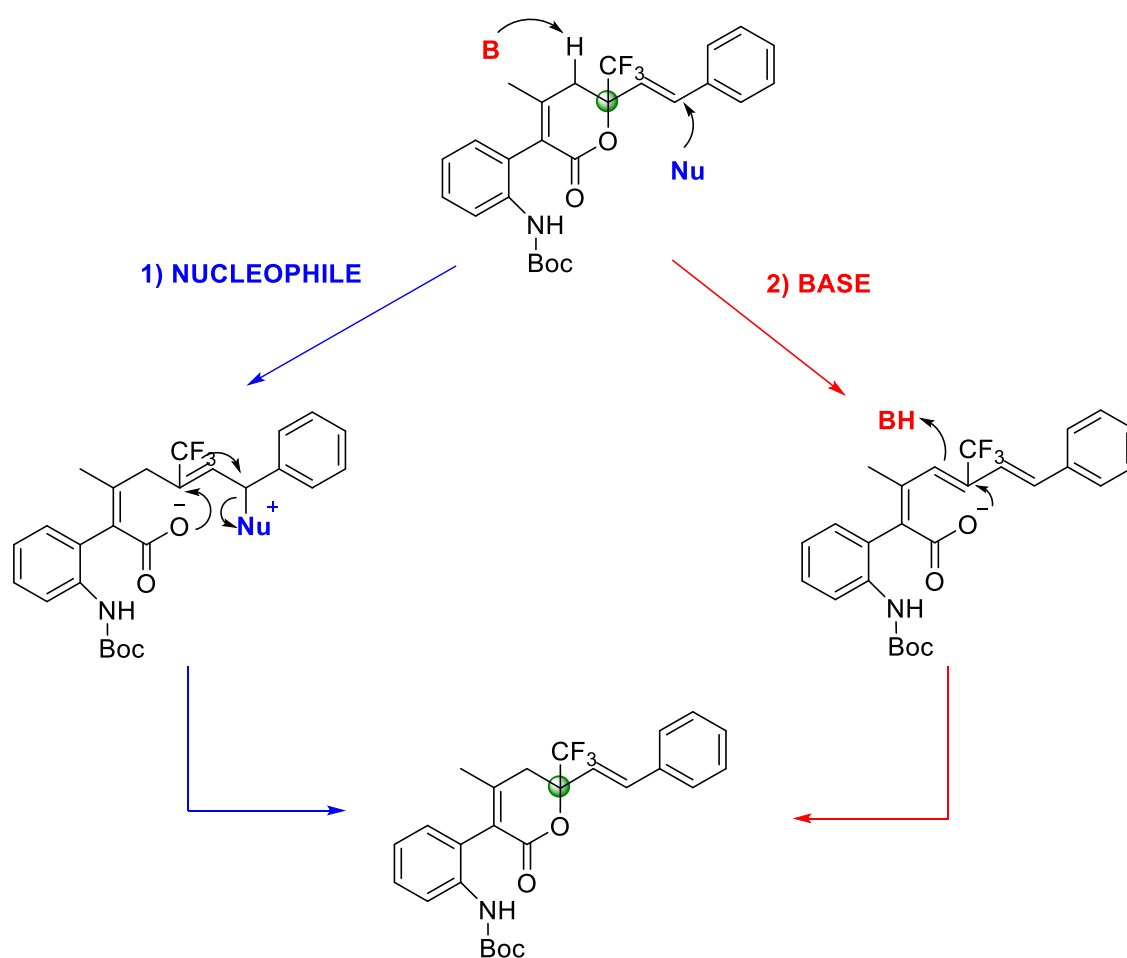


entry	time (days)	ee <b>3</b> (%) <sup>a</sup>
1	1	75
2	2	77
3	6	-

<sup>a</sup>Enantiomeric excess were determined through chiral HPLC.

From the data reported in table 10, it is possible to note that, after 24 h, the racemic mixture **3**, in the presence of catalyst **5c**, undergo enantioenrichment (ee = 75 %, entry 1). After 2 days, the formation of the open 1,2-addition product **4** was observed but the ee of **3** remained almost unchanged (77%). The sixth day, the enantiomeric excess of **3** is not determinable, indeed, compound **3** was completely converted in the open product **4**.

We supposed that the enantiomeric-enrichment is due to the catalyst, which open and close the lactone ring interconverting one enantiomer of **3** into the other. Probably, the two enantiomers of **3** react with different rates with the chiral catalyst, resulting in an enantioenriched mixture. Besides, after 2 days the catalyst yet started to convert the cyclic product **3** in the open one (**4**). In order to investigate if the ring-opening of **3** was caused by the basic or the nucleophilic behaviour of the catalyst (Scheme 35), two different tests were conducted on the enantio-enriched product **3**.



**Scheme 35:** Possible ways of ring-opening with the presence of a nucleophile or a base.

Firstly, we controlled, by chiral HPLC, the enantiomer excess of a mixture of enantio-enriched **3** (ee = 91 %) and PPh<sub>3</sub> (equivalent ratio 1:1) in DCM (Table 11). Indeed, triphenylphosphine (PPh<sub>3</sub>) is an organophosphorus compound which is widely used in organic synthesis for its nucleophilic character. Even



after 6 days (entry 3), the ee (%) remained unaltered and hence we concluded that the nucleophilic behaviour of the catalyst did not influence the enantiomeric excess.

**Table 11:** Effect on the ee **3** (%) with the presence of PPh<sub>3</sub>.

**Enant-3 (ee = 91 %) + PPh<sub>3</sub>**

entry	time (days)	ee <b>3</b> (%) <sup>a</sup>
1	1	91
2	5	91
3	6	91

<sup>a</sup>Enantiomeric excess were determined through chiral HPLC

Secondly, the influence of the basic behaviour of the catalyst on the ee **3** (%) was examined. For this purpose, the enantiomer excess of a mixture of enantio-enriched **3** and K<sub>2</sub>CO<sub>3</sub> (equivalent ratio 1:1) in DCM was monitored by chiral HPLC (Table 12).

**Table 12:** Effect on the ee **3** (%) with the presence of K<sub>2</sub>CO<sub>3</sub>.

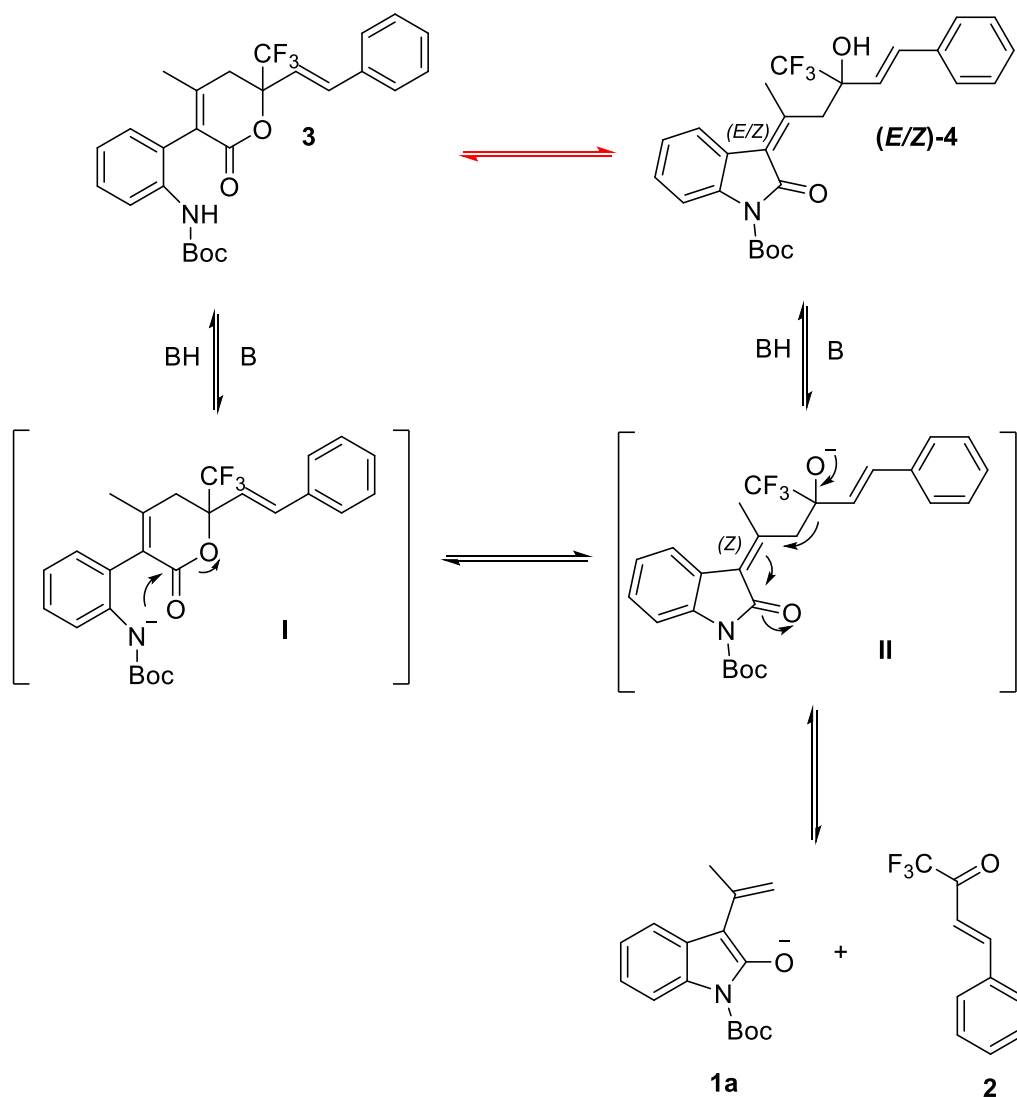
**Enant-3 (ee = 75 %) + K<sub>2</sub>CO<sub>3</sub>**

entry	time (days)	ee (%) <sup>a</sup>
1	1	59
2	2	19
3	6	-

<sup>a</sup>Enantiomeric excess were determined through chiral HPLC

After 1 day, the ee (%) significantly declined from 75 % to 59 %. The second day (entry 2), the cyclic product **3** started to be converted in the opened one (**4**) and, additionally, the ee (%) diminished to 19 %. The sixth day (entry 3), compound **3** was completely converted in the open product **4** and, for this reason, the enantiomer excess of **3** was not determinable. Consequently, we deduced that the basic moiety of the bifunctional chiral catalyst affects the enantiomer excess

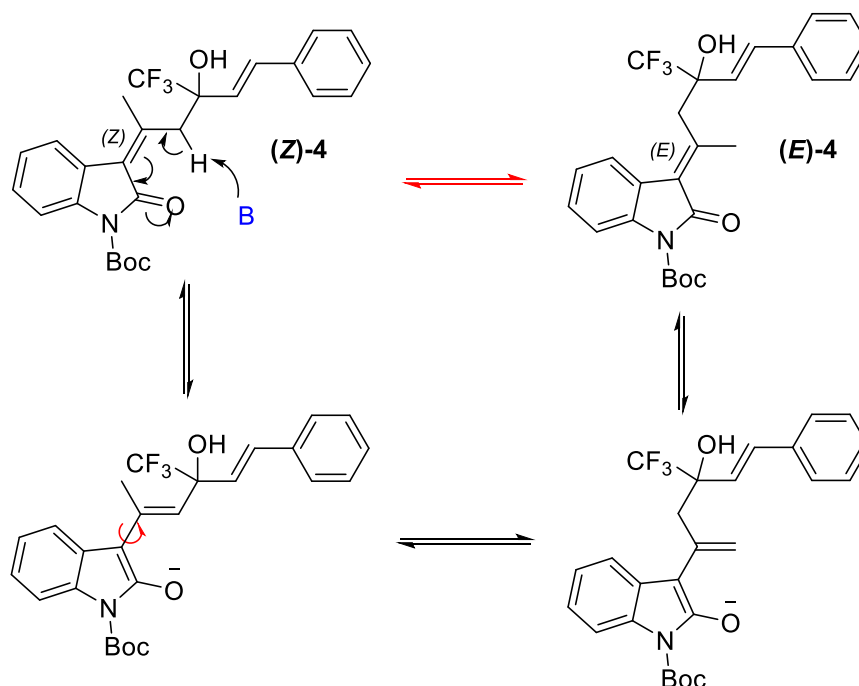
of product **3** and actively contributes to the formation of product **4**. Additionally, we hypothesised an equilibrium between the cyclic product **3** and the open one **4**, illustrated in Scheme 36.



**Scheme 36:** Hypothesized equilibrium between the cyclic product **3** and the open one **4**.

From the experimental evidence (TLC analysis) we supposed that unsaturated lactone **3** is the first product formed. As soon as compound **3** is produced, the basic functionality of the catalyst removes its acidic proton, creating the closed-intermediate **I**. Afterwards, the negatively-charged nitrogen can attack the carbonyl group, opening the lactone ring (intermediate **II**). The opened-intermediate **II** thus formed is also in equilibrium with the open product **4**. Probably, in the presence of the basic catalyst, compound **(Z)-4** quickly undergo

isomerisation, producing a mixture of (*E*)/(*Z*)-isomers as illustrated in Scheme 37.

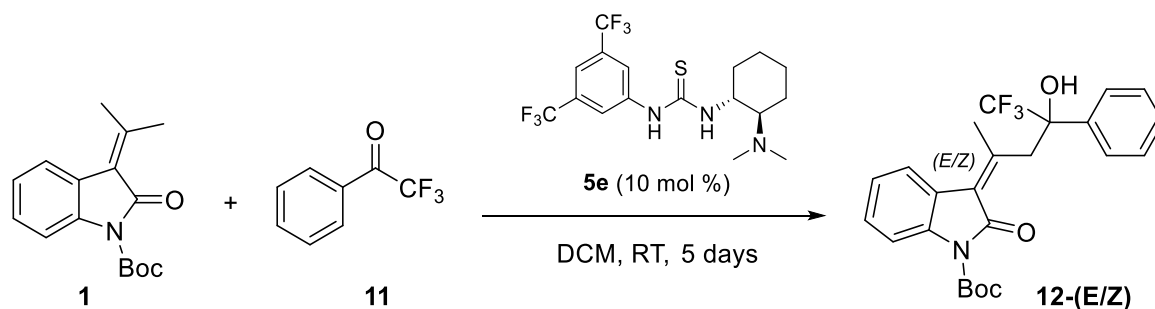


**Scheme 37:** Hypothesized isomerization of product 4 with the presence of the catalyst.

Additionally, intermediate **II** is subjected to retroaldolic reaction, leading to formation of dienolate **1a** and  $\alpha,\beta$ -unsaturated trifluoroketone **2** (scheme 36). Presumably, this equilibrium with the starting reagents could explained the low yield obtained.

### 3.9. REACTIVITY TOWARDS 1,1,1-TRIFLUOROACETOPHENONE

The general scope of the reaction was then investigated by reacting 3-alkylidene oxindole **1** with 1,1,1-trifluoroacetophenone (**11**) (Scheme 38).



**Scheme 38:** Enantioselective vinylogous addition of 3-alkylidene oxindole **1** to 1,1,1-trifluoroacetophenone, under bifunctional catalysis.

Initially, we used as catalyst **5e**, in view of its excellent results in a previous work in which 1,1,1-trifluoroacetophenone was employed as substrate for a cross-aldol reaction<sup>58</sup>. The reactions were monitored through TLC and after 4 days a new product started to form (**12**), even though there was still a consistent amount of unreacted 3-alkylidene oxindole. The fifth day, the reaction was filtered on a thin layer of silica (plug) in order to remove the catalyst. After evaporation of the solvent under reduced pressure, the obtained residue was purified by column chromatography to afford product (**E/Z**)-**12**. The <sup>1</sup>H-NMR, <sup>19</sup>F-NMR, <sup>13</sup>C-NMR and DEPT analysis of compound (**E/Z**)-**12** were consistent with a mixture of (*E*)/(*Z*)-isomers of the 1,2-addition product. In Table 13 the obtained results are reported; all the reactions were carried out on a 0.2 mmol scale.

**Table 13:** Reaction conditions employed for the vinylogous addition between 3-alkylidene oxindole **1** and 1,1,1-trifluoroacetophenone.

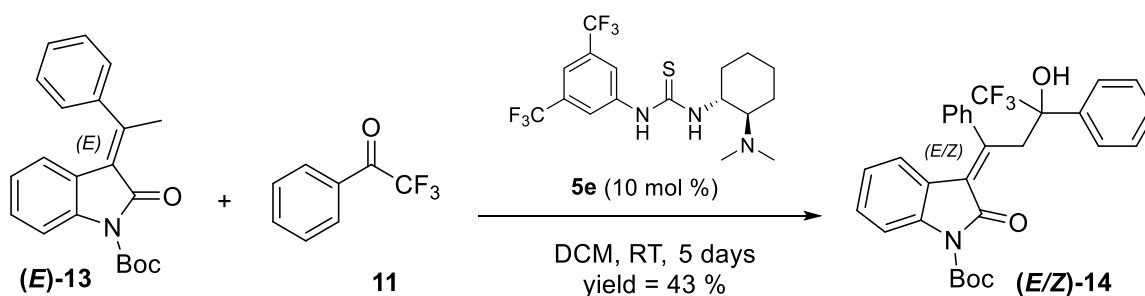
entry <sup>a</sup>	reaction	equivalent 1/2	volume of the solvent (ml)	yield (%) <sup>b</sup>
1	BG067	1:1	1	49
2	BG068	5:1	0,25	19
3	BG073	1:5	0,25	32

<sup>a</sup>All the reactions were interrupted after 5 days. <sup>b</sup>Yield was determined by weighing the purified compounds.

Unfortunately, the best conditions for the separation of the enantiomeric forms of **12** were not founded and therefore it was not possible to assess its enantiomer excess. The best result in terms of yield (49 %) was observed with the reaction

conditions of entry 1. Regarding entry 2, the same reaction condition of a previous work were employed<sup>58</sup>, obtaining a low yield (19 %). In the attempt to afford a reaction product separable through chiral HPLC, we then investigated the reaction between 3-alkylidene oxindole (**E-13**) and 1,1,1-trifluoroacetophenone (Scheme 39), maintaining the same conditions of entry 1 (Table 13). The reaction product **14** was afforded in 43 % yield and, also in this case, its <sup>1</sup>H-NMR, <sup>19</sup>F-NMR, <sup>13</sup>C-NMR and DEPT analysis were consistent with a mixture of (E)/(Z)-isomers. Because of the fact that 3-alkylidene oxindole (**E-13**) possess only one functionalizable  $\gamma$ -position, this results reinforced our hypothesis that, probably, in the presence of the catalyst, also this 1,2-addition product undergo isomerisation.

Unluckily, also chiral HPLC analysis of the product **14** gave negative results and for this reason, we did not focused our attention in the improvement of the reactions yields.

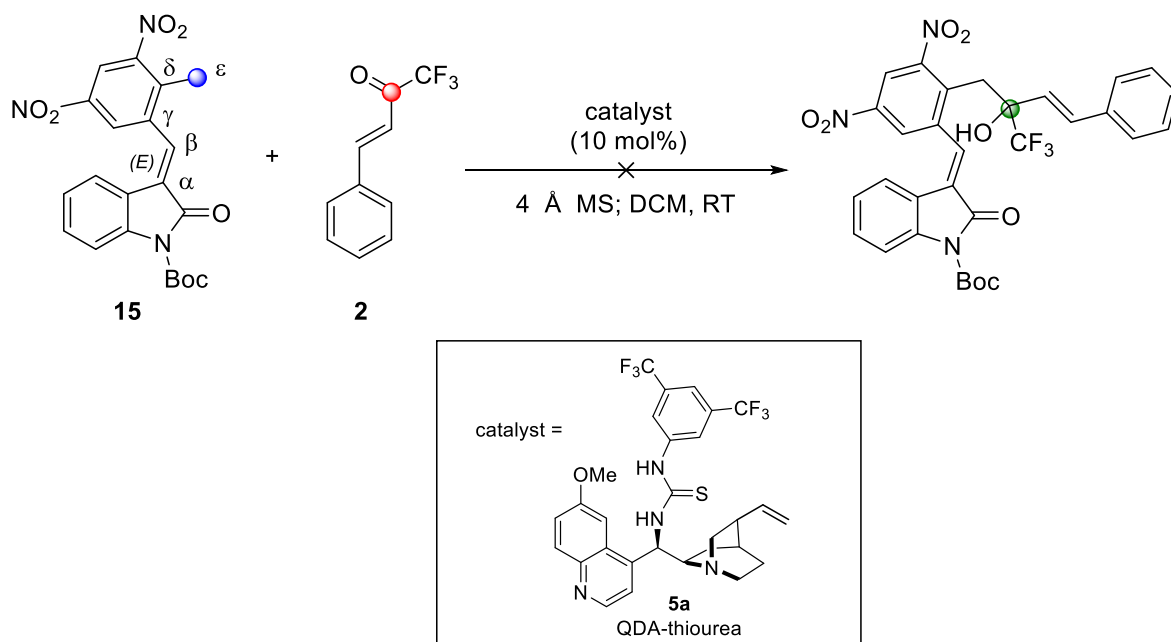


**Scheme 39:** Enantioselective vinylogous addition of 3-alkylidene oxindole (**E-13**) to 1,1,1-trifluoroacetophenone, under bifunctional catalysis.

### 3.10. INVESTIGATIONS ON THE HYPERVINYLOGOUS ADDITION OF 3-ALKYLIDENE OXINDOLES TO UNSATURATED TRIFLUOROMETHYL KETONES

Inspired by the asymmetric benzylation developed by Li and co-workers<sup>57</sup>, we attempted to performed an enantioselective hypervinylogous benzylation of the 3-alkylidene oxindole **15** with the  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2**, using a bifunctional cinchona alkaloid catalyst (**5a**) (Scheme 40). Our aim was to exploit the hypervinylogous reactivity of 3-alkyliden oxindoles in order to obtain  $\epsilon$ -substituted derivatives with a trifluoromethylated carbon stereocenter. Electron-

withdrawing group like NO<sub>2</sub> were introduced on the aromatic ring with the purpose of increasing the pro-nucleophilic character of the alkyl group attached at the ε-position of the ylidene.



**Scheme 40:** Hypervinylogous addition of 3-alkylidene oxindole **15** to  $\alpha,\beta$ -unsaturated trifluoroketone **2**. The enolizable site is indicated in blue, while the electrophilic sites are highlighted in red.

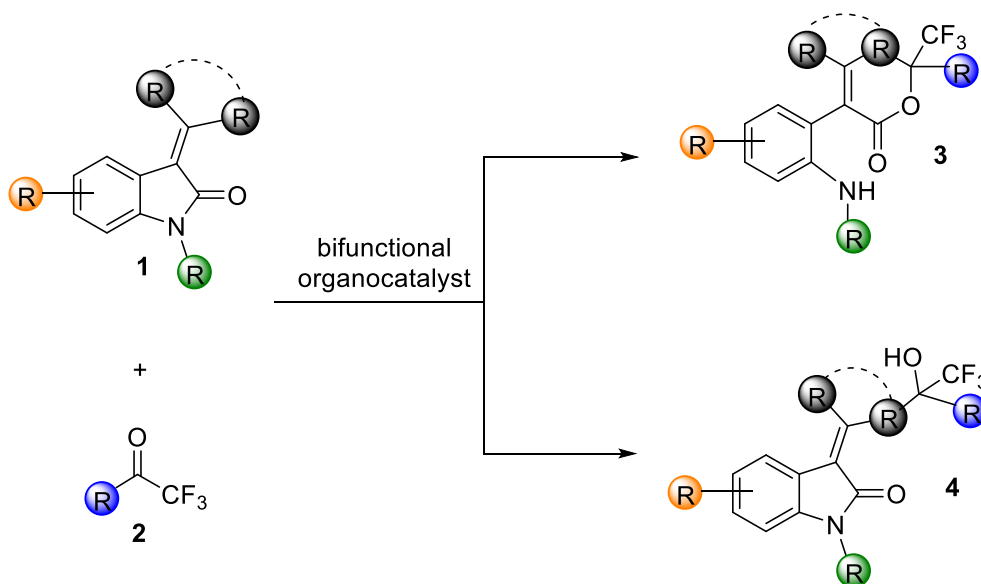
The reaction was carried out in the same standard conditions illustrated in scheme 37 (0.2 mmol scale, equivalent ratio between reagents 1:1). However, the benzylation did not proceed and, even after one week, the TLC analysis revealed only the presence of the starting reagents **15** and **2**.

## 4. CONCLUSIONS AND FUTURE WORK

In summary, we have tried to develop an enantioselective organocatalyzed vinylogous aldol-lactonization of 3-alkylidene oxindole **1** to  $\alpha,\beta$ -unsaturated trifluoromethyl ketone **2**, by using bifunctional organocatalysts. An enantioenriched unsaturated trifluoromethyl lactone **3** with a tetrasubstituted carbon stereocenter is synthesized in moderate yield with high enantioselectivity. Nevertheless, also the two *E/Z* isomers of the vinylogous aldol product **4** are obtained.

In order to find the best reaction condition in terms of yield and enantiomer excess of product **3**, different types of chiral bifunctional organocatalysts and solvents were screened. Afterwards, the dependence of our reaction toward different parameters was examined. Altogether, the best results (yield = 42 % and ee = 93 %) were obtained using DHQA-thiourea **5c** (5 mol %) as catalyst in 0.5 ml of dry THF at room temperature (reaction BG098).

For future related projects, the general substrate scope of both 3-alkylidene oxindoles and trifluoromethyl ketones might be expanded (Scheme 41).



**Scheme 41:** General substrate scope of both 3-alkylidene oxindoles and trifluoromethyl ketones.

## 5. EXPERIMENTAL SECTION

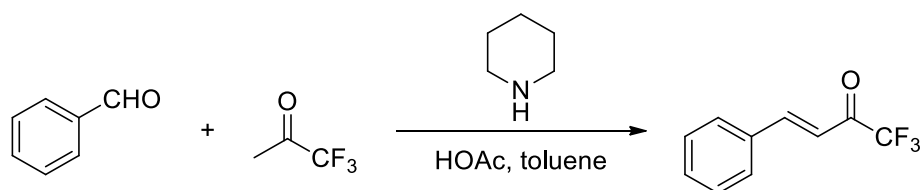
### 5.1 GENERAL INFORMATIONS

$^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR were recorded on spectrometer Varian AS 300, 400 or 600 MHz. Chemical shifts ( $\delta$ ) are reported in ppm using as reference tetramethylsilane (TMS) or the signals of the deuterated solvent ( $\text{CDCl}_3$ ), 7.26 ppm for  $^1\text{H}$ -NMR and 77.0 ppm for  $^{13}\text{C}$ -NMR.  $^{19}\text{F}$ -NMR were recorded on spectrometer Varian AS 400; chemical shifts are reported with respect to an external  $\alpha,\alpha,\alpha$ -trifluorotoluene reference standard (-63.72 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dt = double triplet, m = multiplet, br.s = broad singlet, br.t = broad triplet), coupling constants (Hz), integration. Carbon types were determined from DEPT and  $^{13}\text{C}$  NMR experiments. The separation and purification of compounds were performed through flash chromatography on silica gel 720-230 mesh. Enantiomer excesses (ee) were determined by chiral HPLC analysis with UV spectrophotometric detector on Chiral Pack IC, in comparison with the authentic racemate ( $\lambda = 254 \text{ nm}$ ). All the reactions were monitored through thin layer chromatography (TLC), using silica gel plastic sheets (60F-254) and employing UV light as visualizing agent.

Substrates, reagents and solvents were acquired from common commercial sources and used as received. All the  $\text{CH}_2\text{Cl}_2$  was previously filtered over basic  $\text{Al}_2\text{O}_3$  to remove the ethanol that is used as a stabilizing agent. To obtain dry THF, the solvent was distilled over sodium. Toluene was dried through distillation over sodium.

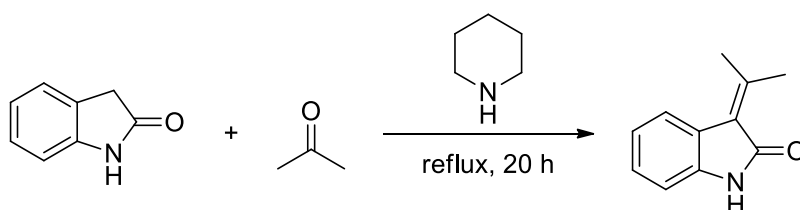


## 5.2. SYNTHESIS OF (*E*)-1,1,1-TRIFLUORO-4-PHENYLBUT-3-EN-2-ONE<sup>60</sup>



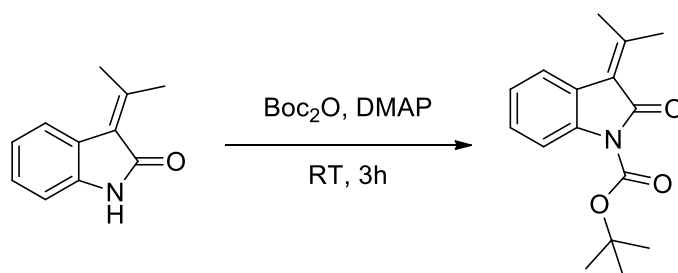
To a stirred solution of benzaldehyde (1.1 g, 10 mmol), acetic acid (0.9 g, 15 mmol), and piperidine (0.9 g, 10 mmol) in dry toluene (10 mL) at 0 °C was added dropwise a solution of 1,1,1-trifluoroacetone (4.5 g, 40 mmol) (10 mL). The mixture was stirred for 2h at this temperature and then 24h at room temperature. After stirring the mixture at room temperature for 12 hours, another 0.9 g of piperidine were added (10 mmol). Subsequently, the reaction was quenched with a saturated aqueous solution of ammonium chloride (10 ml). The organic layer was washed with water and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with *n*-hexane to give 847 mg of the product as a pale yellow oil (yield: 42 %). The product is volatile and it is not recommended to dry it in vacuo.

## 5.3. SYNTHESIS OF SYNTHESIS OF 3-(PROPAN-2-YLIDENE)INDOLIN-2-ONE<sup>58</sup>



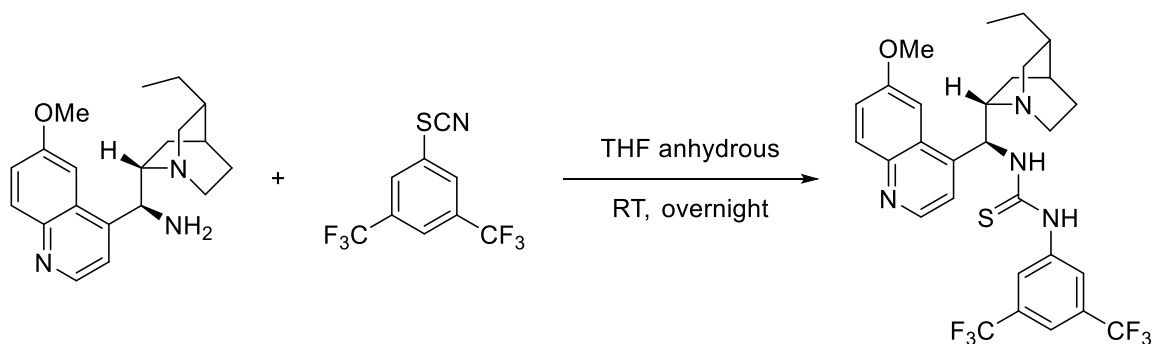
Piperidine (2.5 g, 30 mmol) was added to a stirred solution of indolin-2-one (2 g, 15 mmol) in acetone (30 ml) and the resulting mixture was heated under reflux for 20 hours. After cooling the mixture at room temperature, *n*-hexane (50 ml) was added and the flask was then stored at 0 °C for 4 hours. The pale yellow precipitated formed was recovered by filtration to give 1.79 g of the product as a sand-coloured solid (yield = 69 %).

#### 5.4. SYNTHESIS OF TERT-BUTYL 2-OXO-3-(PROPAN-2-YLIDENE)INDOLINE-1-CARBOXYLATE



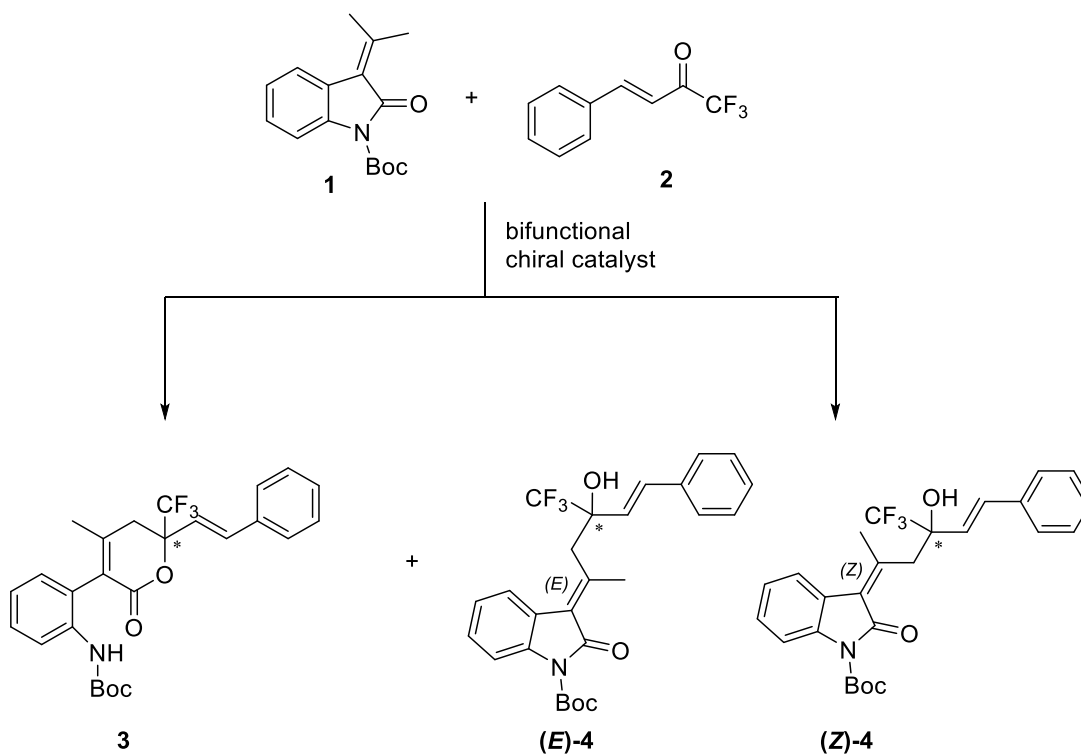
To a stirred solution of 3-(propan-2-ylidene)indolin-2-one (845 mg, 4.88 mmol) in DCM (20 ml) at room temperature were added in order di-tert-butyl-carbonate (1.28 g, 5.85 mmol) and 4-dimethylaminopyridine (60 mg, 0.48 mmol). After 3 hours the reaction can be considered completed and the solvent can be evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of *n*-hexane/ethyl acetate 90:10 to afford 1.1 g of the product as a white solid (yield = 82 %).

#### 5.5. SYNTHESIS OF DIHYDROQUININE THIOUREA



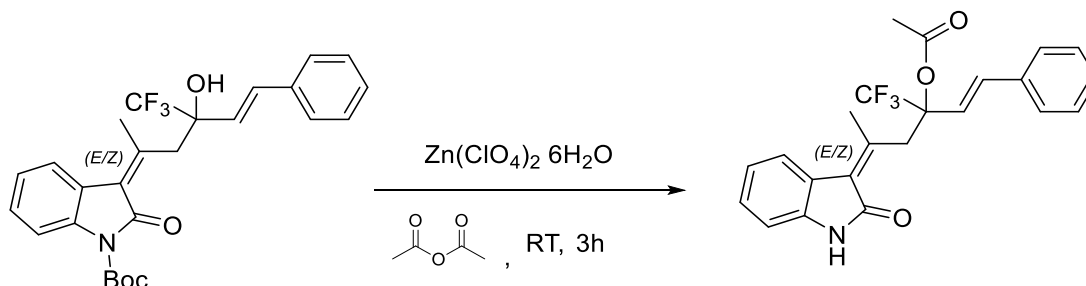
To a stirred solution of 1-thiocyanato-3,5-bis(trifluoromethyl)benzene (0.61 g, 2.24 mmol) in THF anhydrous at room temperature, was added slowly a solution of DHQA-NH<sub>2</sub> (0.61 g, 1.87 mmol) in THF anhydrous (5.5 ml). The mixture was vigorously stirred overnight. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/methanol (95:5) to afford 0.78 g of the final product as a white solid (yield = 70 %).

## 5.6. GENERAL PROCEDURE FOR THE ADDITION BETWEEN 2-OXO-3-(PROPAN-2-YLIDENE)INDOLINE-1-CARBOXYLATE AND (*E*)-1,1,1-TRIFLUORO-4-PHENYLBUT-3-EN-2-ONE



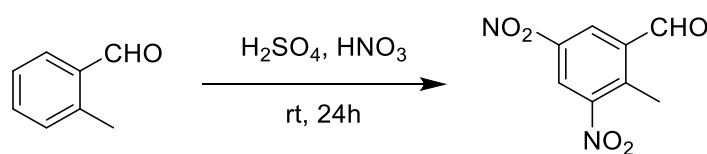
In an ordinary vial equipped with Teflon-coated stir bar were added, at room temperature, (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), 0.5-1 ml of solvent, tert-butyl 2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate (55 mg, 0.2 mmol) and the catalyst (5-10 mol %). When the reaction was considered completed, the crude mixture was flushed through a short plug of silica using DCM/EA 1:1 as the eluent (100 ml). Subsequently the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate 90:10 to afford both the products as colourless oils.

## 5.7. SYNTHESIS OF (*E*)-1,1,1-TRIFLUORO-4-(2-OXOINDOLIN-3-YLIDENE)-2-PHENYLPENTAN-2-YL ACETATE AND (*Z*)-1,1,1-TRIFLUORO-4-(2-OXOINDOLIN-3-YLIDENE)-2-PHENYLPENTAN-2-YL-ACETATE



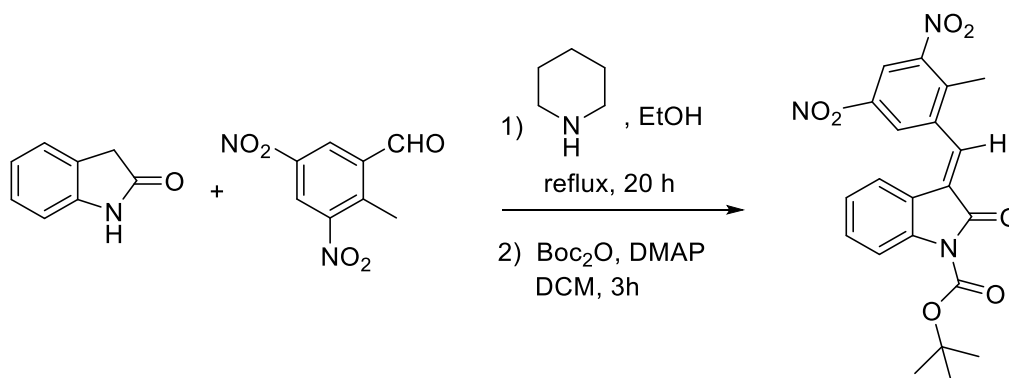
To a stirred solution of (*E/Z*)-tert-butyl 2-oxo-3-(5,5,5-trifluoro-4-hydroxy-4-phenylpentan-2-ylidene)indoline-1-carboxylate (9.5 mg, 0.02 mmol) in acetic anhydride (338  $\mu\text{l}$ ) was added  $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5.2 mg, 0.014 mmol). After 3 hours the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 60:40) to obtain 7 mg of the product as a brown oil (yield = 84 %).

## 5.8. SYNTHESIS OF 2-METHYL-3,5-DINITROBENZALDEHYDE<sup>63</sup>



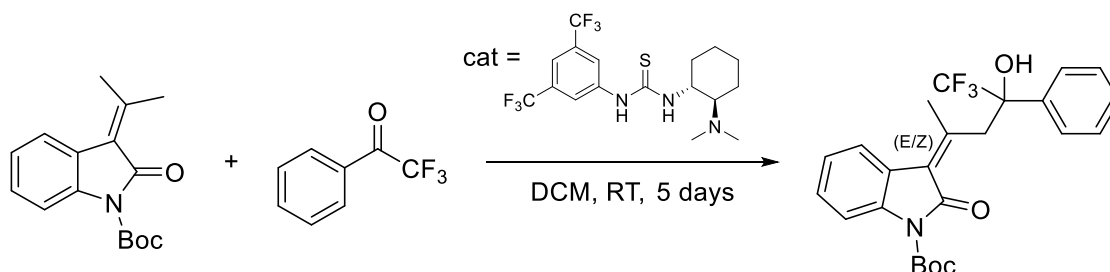
To a stirred solution of 2-methylbenzaldehyde (1.2 g, 10 mmol) in  $\text{H}_2\text{SO}_4$  96% (50 ml) at  $0^\circ\text{C}$  was added dropwise  $\text{HNO}_3$  65% (5 ml). The resulting solution was stirred for 24 h at room temperature until the completion of reaction, as monitored by TLC. Subsequently, the suspension was added dropwise to the ice water (200 mL) with vigorous stirring. After addition was complete, the resulting solid was vacuum-filtered through filter paper and washed with cold water (30 mL). The residue was then dried in vacuo to give 970 mg of the product as a white solid (yield = 46 %).

## 5.9. SYNTHESIS OF (E)-TERT-BUTYL 3-(2-METHYL-3,5-DINITROBENZYLIDENE)-2-OXOINDOLINE-1-CARBOXYLATE



To a stirred solution of indolin-2-one (510 mg, 3.8 mmol) in EtOH (9 ml), were added 2-methyl-3,5-dinitrobenzaldehyde (970 mg, 4.6 mmol) and piperidine (37  $\mu\text{l}$ , 0.38 mmol). The resulting mixture was heated under reflux overnight. After removal of the solvent under reduced pressure, 180 ml of ethyl acetate and 10 ml of a solution 1M of  $\text{KHSO}_4$  were added. The aqueous layer was extracted with ethyl acetate (2 x 40 ml) and the combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ . Subsequently, the solvent was removed under reduced pressure and the residue is solubilised in DCM (15 ml). Di-*tert*-butyl-carbonate (1.2 g, 4.56 mmol) and 4-dimethylaminopyridine (46 mg, 0.38 mmol) were then added and the resulting mixture was stirred at room temperature for 3 hours. After removal of the solvent, the residue was purified by column chromatography on silica gel eluting with a mixture of *n*-hexane/ethyl acetate 90:10 to obtain 700 mg of product as a yellow solid (yield= 43 %).

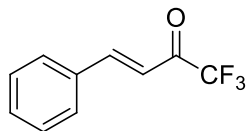
### 5.10. GENERAL PROCEDURE FOR ADDITION BETWEEN 2-OXO-3-(PROPAN-2-YLIDENE)INDOLINE-1-CARBOXYLATE AND 2,2,2-TRIFLUOROACETOPHENONE



In an ordinary vial equipped with Teflon-coated stir bar were added, at room temperature, 2,2,2-trifluoroacetophenone (35 mg, 0.2 mmol), 1ml of DCM, *tert*-butyl 2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate (55 mg, 0.2 mmol) and the Takemoto catalyst (10 mol %). After 5 days the crude mixture was flushed through a short plug of silica using DCM/EA 1:1 as the eluent. Subsequently, after removal of the solvent under reduced pressure, the obtained residue was purified by column chromatography on silica gel eluting with a mixture of *n*-hexane/ethyl acetate 90:10 to give the product as a colourless oil.

## 5.11. DATA OF THE PRODUCTS

### (E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one

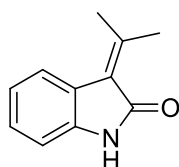


<sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: -77.6 (s, 3F).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.98 (d, *J* = 16.4 Hz, 1H), 7.65 (m, 2H), 7.54-7.41 (m, 3H), 7.02 (d, *J* = 16.1 Hz, 1H).

<sup>13</sup>C-NMR (100 Hz, CDCl<sub>3</sub>) δ: 180.0, 150.2, 133.4, 132.3, 129.2, 116.7, 116.4.

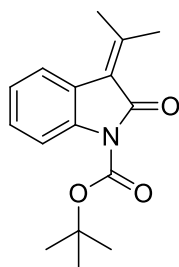
### 3-(propan-2-ylidene)indolin-2-one



<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 9.06 (br.s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.18 (br.t, *J* = 7.7 Hz, 1H), 7.02 (td, *J*<sub>1</sub> = 7.7 Hz, *J*<sub>3</sub> = 1.0 Hz, 1H), 6.91 (td, *J*<sub>1</sub> = 7.7 Hz, *J*<sub>2</sub> = 1.0 Hz, 1H), 2.59 (s, 3H), 2.39 (s, 3H).

<sup>13</sup>C-NMR (100 Hz, CDCl<sub>3</sub>) δ: 170.0, 155.4, 139.6, 127.4, 124.3, 123.5, 123.1, 121.4, 109.4, 25.2, 23.0.

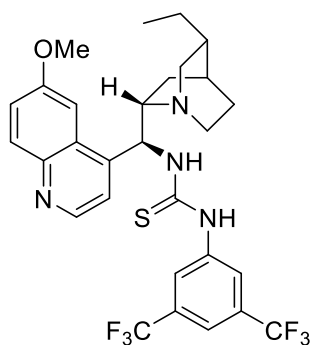
### Tert-butyl 2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate



<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.89 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 2.61 (s, 3H), 2.40 (s, 3H), 1.66 (s, 9H).

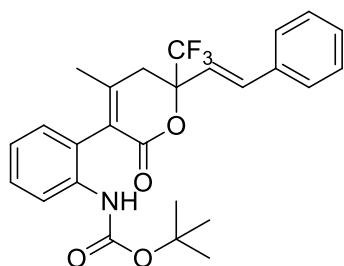
<sup>13</sup>C-NMR (100 Hz, CDCl<sub>3</sub>) δ: 165.4, 156.7, 149.6, 137.8, 127.6, 124.0, 123.5, 123.1, 121.6, 114.4, 83.8, 28.1, 25.9, 24.1.

## Dihydroquinine thiourea



$^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.69 (d,  $J = 4.72$  Hz, 1H), 8.10 (br.s, 3H), 7.95 (d,  $J = 9.26$  Hz, 1H), 7.59 (s, 1H), 7.57 (d,  $J = 4.87$  Hz, 1H), 7.45 (dd,  $J_1 = 9.29$  Hz,  $J_2 = 2.68$  Hz, 1H), 6.37 (d,  $J = 9.89$  Hz, 1H), 4.03 (s, 3H), 3.61 (m, 1H), 3.41 (m, 1H), 7.88 (d,  $J = 8.22$  Hz, 1H), 3.30 (m, 1H), 2.83 (m, 1H), 2.54 (m, 1H), 1.72 (m, 2H), 1.54 (m, 1H), 1.40 (m, 1H), 1.35 (m, 3H), 0.86 (t,  $J = 7.35$  Hz, 3H), 0.70 (m, 1H).

## (*E*)-tert-butyl (2-(4-methyl-2-oxo-6-styryl-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-3-yl)phenyl)carbamate



$^{19}\text{F-NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -81.3 (s, 3F).

$^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.84 (d,  $J = 8.2$  Hz, 1H), 7.50 (d,  $J = 8.2$  Hz, 1H), 7.40 (m, 2H), 7.36-7.25 (m, 4H), 7.15 (br.t,  $J = 7.7$  Hz, 1H), 6.92 (d,  $J = 15.8$  Hz, 1H), 6.27 (d,  $J = 15.8$  Hz, 1H), 5.39 (s, NH), 4.35 (d,  $J = 12.6$  Hz, 1H), 2.83 (d,  $J = 12.6$  Hz, 1H), 2.35 (s, 3H), 1.66 (s, 9H).

$^{13}\text{C-NMR}$  (100 Hz,  $\text{CDCl}_3$ ): 168.7, 152.5, 148.8, 138.2, 135.9, 133.0, 128.7, 128.6, 128.1, 126.8, 124.3, 124.1, 123.7, 123.3, 114.7, 85.0, 78.0 (q,  $J = 28$  Hz,  $\text{CF}_3$ ), 42.0, 28.1, 27.9.

**HPLC conditions:** column: Chiral Pack IC, eluent: 95:5 *n*-hexane/isopropanol, flux: 1 ml/min,  $\lambda = 254$  nm

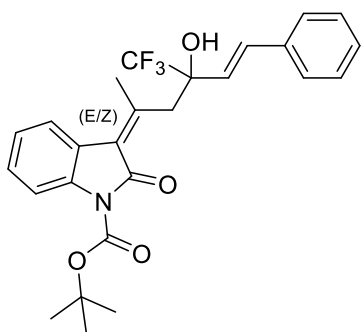


**Table 14:** Enantiomeric excess obtained with different bifunctional catalysts.

entry	reaction	catalyst	time (d)	ee 3 (%) <sup>a</sup>
1	BG045	5a	2	-87
2	BG046	5b	4	63
3	BG066	5c	1	91
4	BG059	5d	4	65
5	BG060	5e	4	80
6	BG061	5f	4	-75
7	BG062	5g	4	-
8	BG063	5h	4	-
9	BG064	5i	4	-
10	BG084	5l	1	91
11	BG085	5m	4	-
12	BG086	5n	4	-

<sup>a</sup>Enantiomeric excess were determined through chiral HPLC (retention times ( $t_R$ ): enantiomer A= 5.6min.; enantiomer B=7.0 min.).

**(E)-tert-butyl-3-((E)-4-hydroxy-6-phenyl-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate and (Z)-tert-butyl-3-((E)-4-hydroxy-6-phenyl-4-(trifluoromethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate**

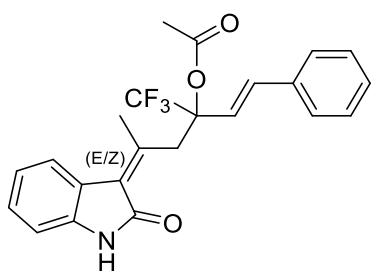


<sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: -79.8 (s, 3F), -79.9 (s, 3F).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.89 (d,  $J$  = 8.4 Hz, 1H), 7.46-7.30 (m, 5H), 7.12 (m, 1H), 7.05-6.94 (m, 2H), 6.78 (dd,  $J_1$  = 7.7 Hz,  $J_2$  = 1.6 Hz, 1H), 6.47 (bs, OH, isomer *E* or *Z*, 0.5H), 6.23 (d,  $J$  = 16.0 Hz, 0.5 H), 6.17 (d,  $J$  = 16.0 Hz, 0.5H), 6.04 (bs, OH, isomer *Z* or *E*, 0.5H), 3.31-3.20 (m, 1H), 2.87 (d,  $J$  = 18.2 Hz, isomer *E* or *Z*, 0.5H), 2.80 (d,  $J$  = 18.2 Hz, 1H, isomer *Z* or *E*, 0.5H), 1.87 (s, 1.5

H, isomer *E* or *Z*), 1.83 (s, 1.5 H, isomer *Z* or *E*), 1.49 (s, 5H, isomer *E* or *Z*), 1.27 (s, 4H, isomer *Z* or *E*).

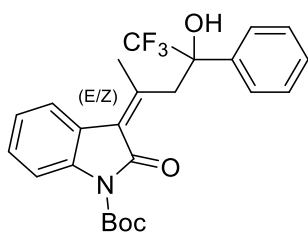
**(*Z*)-1,1,1-trifluoro-4-(2-oxoindolin-3-ylidene)-2-phenylpentan-2-yl acetate and (*E*)-1,1,1-trifluoro-4-(2-oxoindolin-3-ylidene)-2-phenylpentan-2-yl acetate**



<sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: -80.0 (s, 3F), -79.8 (s, 3F).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 7.91-7.81 (m, 1H), 7.52 (bs, 0.5H), 7.47-7.33 (m, 5H), 7.24-7.17 (m, 0.5H), 7.16-7.00 (m, 1.5H), 6.92 (d, *J* = 15.5 Hz, 0.5H), 6.83 (d, *J* = 7.6 Hz, 0.5H), 6.77 (bs, 0.5H, isomer *Z* or *E*), 6.27 (d, *J* = 16.5 Hz, 0.5H), 6.17 (d, *J* = 16.0 Hz, 0.5H), 3.31-3.20 (m, 1H), 2.88-2.77 (m, 1H), 2.10 (s, 1.5H), 1.88 (s, 1.5H), 1.85 (s, 1.5H).

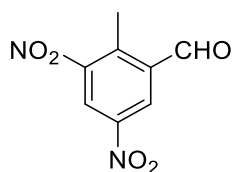
**(*Z*)-tert-butyl-2-oxo-3-(5,5,5-trifluoro-4-hydroxy-4-phenylpentan-2-ylidene)indoline-1-carboxylate and (*E*)-tert-butyl-2-oxo-3-(5,5,5-trifluoro-4-hydroxy-4-phenylpentan-2-ylidene)indoline-1-carboxylate**



<sup>19</sup>F-NMR: (376 MHz, CDCl<sub>3</sub>) δ: -79.5 (s, 3F), -79.3 (s, 3F).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.85 (d, *J* = 8.3 Hz, 0.5H), 7.80 (d, *J* = 8.3 Hz, 0.5H), 7.67-7.44 (m, 5H), 7.32-7.24 (m, 1H), 7.14-7.05 (m, 1H), 6.89 (td, *J*<sub>1</sub> = 7.6 Hz, *J*<sub>2</sub> = 1.2 Hz, 0.5H), 6.56 (bs, 0.5H, isomer *E* or *Z*), 6.19 (dd, *J*<sub>1</sub> = 7.6 Hz, *J*<sub>2</sub> = 1.5 Hz, 0.5H), 5.20 (bs, 0.5H, isomer *Z* or *E*), 3.48-3.39 (m, 1H), 3.19 (t, *J* = 18.3 Hz, 1H), 1.8 (s, 1.5H, isomer *E* or *Z*), 1.74 (s, 1.5H, isomer *Z* or *E*), 1.50 (s, 5H, isomer *E* or *Z*), 1.43 (s, 4H, isomer *Z* or *E*).

## 2-methyl-3,5-dinitrobenzaldehyde

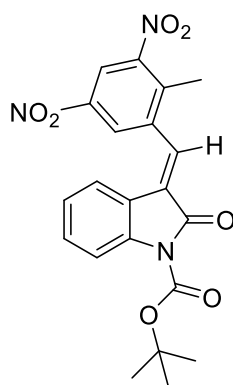


$^1\text{H-NMR}$  (**400 MHz**,  $\text{CDCl}_3$ )  $\delta$ : 10.41 (s, 1 H), 8.85 (d,  $J = 2.4$  Hz, 1 H), 8.81 (d,  $J = 2.4$  Hz, 1 H), 2.91 (s, 3 H).

$^{13}\text{C-NMR}$  (**100 MHz**,  $\text{CDCl}_3$ )  $\delta$ : 188.0, 151.9, 146.2, 140.6, 137.0, 128.3, 123.0, 14.6.

## (*E*)-tert-butyl 3-(2-methyl-3,5-dinitrobenzylidene)-2-oxoindoline-1-carboxy.

late



$^1\text{H-NMR}$  (**400 MHz**,  $\text{CDCl}_3$ )  $\delta$ : 8.74 (d,  $J = 2.5$  Hz, 1H), 8.55 (d,  $J = 2.5$  Hz, 1H), 7.96 (d,  $J = 8.1$  Hz, 1H), 7.75 (s, 1H), 7.42-7.35 (m, 1H), 7.01-6.90 (m, 2H), 2.59 (s, 3H), 1.68 (s, 9H).

$^{13}\text{C-NMR}$  (**100 MHz**,  $\text{CDCl}_3$ ): 165.1, 150.9, 148.8, 145.9, 140.9, 139.1, 138.7, 131.7, 130.6, 130.5, 126.4, 124.4, 122.4, 119.9, 119.7, 115.8, 84.9, 28.1, 16.8.

## 6. REFERENCES

- 
- <sup>1</sup> Pasteur, L.; *La dissymétrie moléculaire*, OEuvres de Pasteur, 1922, **1**, Masson, Paris, 21.
- <sup>2</sup> Lenz, W.; Pfeiffer, R. A.; Kosenow, W.; Hayman, D. J.; *Lancet*, 1962, **279**, 45-46.
- <sup>3</sup> Knowles W. S.; *Angew. Chem. Int. Ed.*; 2002, **41**, 1998- 2007.
- <sup>4</sup> Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R.; *Org. Synth.*; 1993, **71**,1.
- <sup>5</sup> MacMillan D.W.C.; *Nature*, 2008, **455**, 304-30.
- <sup>6</sup> Hajos, Z.G.; Parrish, D.R.; *J. Org. Chem*, 1974, **39**, 1615–1621.
- <sup>7</sup> Hajos, Z.G.; Parrish, D.R.; *German patent* DE 2102623, 1971.
- <sup>8</sup> Eder, U.; Sauer, G. R.; Wiechert, R.; *German patent* DE 2014757, 1971.
- <sup>9</sup> Tu, Y.; Wang, Z.; Shi, Y.; *J. Am. Chem. Soc.*; 1996, **118**, 9806–9807.
- <sup>10</sup> Denmark, S. E.; Wu, Z.; Crudden, C.; Matsushashi, H.; *J. Org. Chem.* 1997, **62**, 8288–8289.
- <sup>11</sup> Sigman, M.; Jacobsen, E. N.; *J. Am. Chem. Soc.*; 1998, **120**, 4901–4902.
- <sup>12</sup> Corey, E. J.; Grogan, M. J.; *Org. Lett.*; 1999, **1**, 157–160.
- <sup>13</sup> List, B.; Lerner, R. A.; Barbas, C. F.; *J. Am. Chem. Soc.*; 2000, **122**, 2395–2396.
- <sup>14</sup> Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C.; *J. Am. Chem. Soc.*; 2000, **122**, 4243– 4244.
- <sup>15</sup> List, B.; *Chem. Commun.* 2006, 819-824.
- <sup>16</sup> Bui, T.; Barbas, C.F.; *Tetrahedron Lett.* 2000, **41**, 6951-6954.
- <sup>17</sup> Bertelsen, S.; Marigo, M.; Brandes, S.; Dine, P.; Jørgensen, K. A.; *J. Am. Chem. Soc.*; 2006, **128**, 12973-12980.
- <sup>18</sup> Beeson, T.D.; Mastracchio, A.; Hong, J.B.; Ashton, K.; MacMillan, D.W.C.; *Science*, 2007, **316**, 582-585.
- <sup>19</sup> Song, C.E.; cinchona alkaloids in synthesis and catalysis, 2009, (ed C. E. Song), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.
- <sup>20</sup> Bernardi, L.; organocatalisi asimmetrica con interazioni deboli, *La chimica e l'industria*, 2011, 96-103.
- <sup>21</sup> Pasteur, L.; *Acad. Sci.*; 1853, **37**,162.
- <sup>22</sup> Bredig, G; Fiske, P.S.; *Biochem.Z.*; 1912, **46**, 7.

- 
- <sup>23</sup> Pracejus, H.; *Justus Liebigs Ann. Chem.*; 1960, **634**, 9.
- <sup>24</sup> Wynberg, H.; *Top Stereochem*, 1986, **16**, 87.
- <sup>25</sup> Yoon, T. P.; Jacobsen, E. N.; *Science*, 2003, **299**, 1691.
- <sup>26</sup> Madarász, A.; Dósa, Z.; Varga, S.; Soós, T.; Csámpai, A.; Pápai, I.; *ACS catal.*, 2016, **6**, 4379.
- <sup>27</sup> Sigman, M. S.; Jacobsen, E. N.; *J. Am. Chem. Soc.*, 1998, **120**, 4901.
- <sup>28</sup> Schreiner, P. R.; Wittkopp, A.; *Org. Lett.*; 2002, **4**, 217–220.
- <sup>29</sup> Okino, O.; Hoashi, Y.; Takemoto, Y.; *J. Am. Chem. Soc.*; 2003, **125**, 12672-12673.
- <sup>30</sup> Fuson, R. C.; the principle of vinylogy, *Chem. Rev.*; 1935, **16**, 1-27.
- <sup>31</sup> Jia, Z. J.; Jiang, H.; Li, J. L.; Gschwend, B.; Li, Q. Z.; Yin, X.; Grouleff, J.; Chen, Y.C.; Jørgensen, K.A.; *J. Am. Chem. Soc.*; 2011, **133**, 5053-5061.
- <sup>32</sup> Higuchi, K.; Kawasaki, T.; *Nat. Prod. Rep.*; 2007, **24**, 843.
- <sup>33</sup> Singh, G.S.; Desta, Z. Y.; *Chem. Rev.*, 2012, **112**, 6104-6155.
- <sup>34</sup> Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stukey, J.; Krajewski, K.; Roller, P. P.; Wang, S. J.; *J. Med. Chem.*; 2006, **49**, 3432-3435.
- <sup>35</sup> a) Tang, P. C.; Miller, T.; Li, X.; Sun, L.; Wei, C.C; Shirazian, S.; Liang, C.; Vojkovsky, T.; Nematalla, A.; Hawley, M. *Chem. Abstr.* **2001**, 135, 195497; b) Faivre, S.; Demetri, G.; Sargent, W.; Raimond, E.; *Nature Rev. Drug Discovery*, 2007, **6**, 734-745.
- <sup>36</sup> a) Trost, B. M.; Cramer, N.; Bernsmann, H.; *J. Am. Chem. Soc.*; 2007, **129**, 3086-3087; b) Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M. P.; Bartoli, G.; Melchiorre, P.; *Angew. Chem.*; 2009, **121**, 7336-7339; c) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G.; *Chem. Eur. J.*; 2011, **17**, 2842 – 2845 d) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K.; *Org. Biomol. Chem.*; 2012, **10**, 516; e) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, 355, 1023; f) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F. III, *RSC Adv.*; 2014, **4**, 743.
- <sup>37</sup> Battistini, L.; Curti, C.; Rassu, G.; Sartori, A.; Zanardi, F.; *Synthesis*, 2017, **49**, 2297-2336.
- <sup>38</sup> Selvakumar, K.; Vaithyanathan, V.; Shanmugam, P., *Chem. Commun.*; 2010, **46**, 2826.

- 
- <sup>39</sup> Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G.; *Angew. Chem. Int. Ed.*, 2012, **51**, 6200-6204.
- <sup>40</sup> Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R.; *Org. Lett.*, 2014, **16**, 1394.
- <sup>41</sup> Di Iorio, N.; Righi, P.; Ranieri, S.; Mazzanti, A.; Margutta, R. G.; Bencivenni, G.; *J. Org. Chem.*; 2015, **80**, 7158–7171.
- <sup>42</sup> Xiao, X.; Mei, H.; Chen, Q.; Zhao, X.; Lin, L.; Liu, X.; Feng, X. *Chem. Commun.* 2015, **51**, 580.
- <sup>43</sup> Liu, Y.; Yang, Y.; Huang, Y.; Xu, X. H.; Qing, F.; *L. Synlett.*; 2015, **26**, 67-72
- <sup>44</sup> Feng, J. J.; Li, X.; Cheng, J. P.; *Chem. Commun.*; 2015, **51**, 14342.
- <sup>45</sup> Feng, J.; Xin L.; Chen; J.-P.; *J. Org. Chem.*; 2017, **82**, 1412-1419.
- <sup>46</sup> Han, J. L.; Chang, C. H.; *Chem. Commun.*; 2016, **52**, 2322.
- <sup>47</sup> Nenajdenko, G.; Smolko, K. I.; Balenkova, E. S.; *Tetrahedron:Asymmetry*, 2001, **12**, 1259–1266.
- <sup>48</sup> Deng, Y.-H.; Chen, J.-Q.; Kang, L.H and T.-R.; Liu, Q.-Z.; Luo, S.-W.; Yuan, W.-C.; *Chem. Eur. J.* 2013, **19**, 7143–7150.
- <sup>49</sup> Zheng, Y.; Li, Y.; Yang, H.; Wang, H.; Cui, J.; Zhang, G.; Zhao, L.; *Adv.Synth. Catal.*; 2009, **351**,1685–1691.
- <sup>50</sup> Pei, Z.-K.; Zheng, Y.; Ma, J .N and J.-A; *Tetrahedron Lett.*; 2010, **51**, 4658–4661
- <sup>51</sup> Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D.J.; Smith, A. D.; *Chem. Sci.*; 2013, **4**, 4146–4155.
- <sup>52</sup> JindianDuan, Yuyu Cheng, Jing Cheng, Rou Li, and Pengfei Li, *Chem. Eur. J.*; 2017, **23**, 519-523.
- <sup>53</sup> Czerwin, P.; Sky, M.; Molga, E.; Cavallo, L.; Poater, A.; Michalak, M.; *Chem. Eur. J.*; 2016, **22**, 8089–8094.
- <sup>54</sup> Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V.; *Chem. Soc. Rev.*; 2008, **37**, 320–330.
- <sup>55</sup> Fandrick, D. R.; Reeves, J. T.; Bakonyi, J.M.; Nyalapatla, P. R.; Tan, Z.; Niemeier, O.; Akalay, D.; Fandrick, K.R.; Wohlleben, W.; Ollenberger, S.; Song, J. J.; Sun, X.; Qu, B.; Haddad, N.; Sanyal, S.; Shen, S.; Ma, S.; Byrne, D.; Chitroda, A.; Fuchs, V.; Narayanan, B. A.; Grinberg, N.; Lee, H.; Yee, N.; Brenner, M.; Enanayake, C.H.S.; *J. Org. Chem.*; 2013, **78**, 3592–3615.

- 
- <sup>56</sup> Li, P.; Chai, Z.; Zhao, S-L.; Yang, Y-Q.; Wang, H-F.; Zheng, C-W.; Cai, Y-P.; Zhao, G.; Zhu S-Z.; *Chem. Commun.*, 2009, 7369–7371.
- <sup>57</sup> Duan, J.; Cheng, Y.; Cheng, J.; Li, R.; Li, P.; *Chem. Eur. J.*; 2017, **23**, 519–523.
- <sup>58</sup> Wang, P.; Li, H. F.; Zhao, J. Z.; Du, Z. H.; Da, C. S.; *Org. Lett.*, 2017, **19** (10), 2634–2637.
- <sup>59</sup> Patent EP805147A1, (1997), “Lilly industries limited”
- <sup>60</sup> Czerwiński, P.; Molga, E.; Cavallo, L.; Poater, A.; Michalak, M.; *Chem. Eur. J.*, **22**, 2016, 8089-8094.
- <sup>61</sup> A. Pettinato “Sintesi di nuovi diidropiranoni-spiroosindoli attraverso una tandem organocatalizzata di alchilidenossindoli ed isatine” Master’s thesis, Alma Mater Studiorum – University of Bologna, AA 2014-2015, second session.
- <sup>62</sup> J. Alemà, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.*, 2011, 17, 6890–6899.
- <sup>63</sup> Raja, R.; Hong, B.-C.; Lee, G.-H.; *Org. Letters*, 2015, **16**, 5756-5759.





---

## **RINGRAZIAMENTI**

*Alla fine di questo percorso, vorrei ringraziare la Dottoressa Emanuela Marotta, il Dottor Giorgio Bencivenni, il Professore Paolo Righi e il Professore Claudio Paolucci per avermi dato la possibilità di crescere, sia a livello professionale ma anche personale, all'interno del loro gruppo di ricerca. Li ringrazio particolarmente per la fiducia e il supporto che mi hanno dato durante l'intero tirocinio.*

*Inoltre ringrazio i miei compagni di laboratorio Simone Crotti, Nicola Di Iorio e Nicola Martorelli per l'incoraggiamento, per l'aiuto datomi e per i bei momenti condivisi insieme che mi mancheranno moltissimo.*